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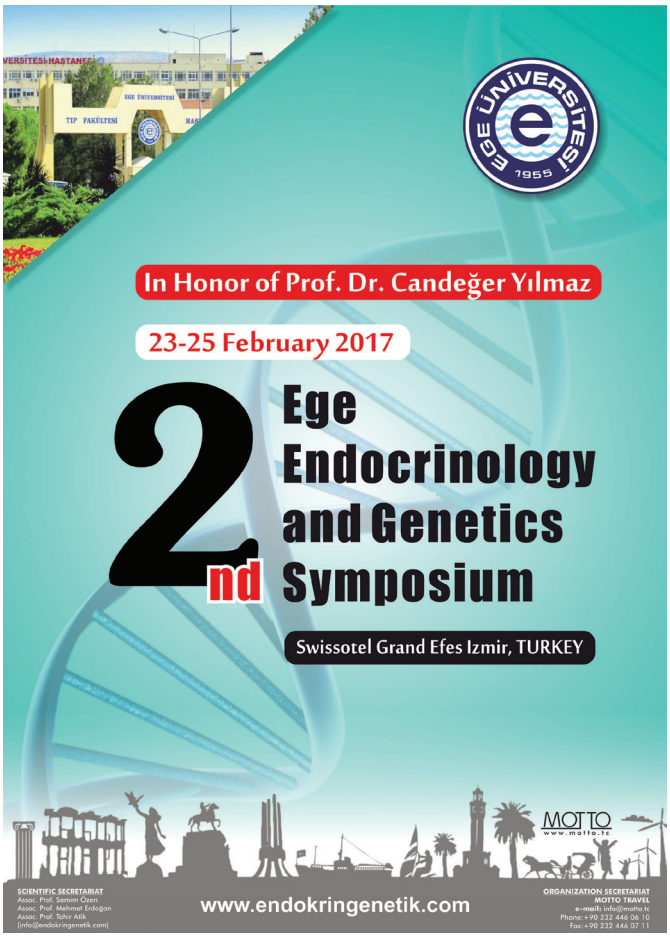

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Dear Colleagues,

In this issue, we would like to publish abstracts that were presented in the 2nd Endocrine Diseases and Genetics Symposium, İzmir. This symposium has been organized in February 23-25, 2017.

The use of genetic technology in the diagnosis and management of endocrine diseases is increasing day by day in the way of sharing information among disciplines in diseases. In the 2nd Endocrine Diseases and Genetics Symposium; we aimed to increase our level of knowledge and skills by bringing together our colleagues working in the field of endocrine and genetics.

We believed that this meeting, which we intend to make traditional, would provide an environment in which scientists working in both fields could follow and discuss the latest developments in the world. Our symposium program had a rich scientific content. Medical geneticists have shared many valuable experts, knowledge and experiences in the fields of adult and child endocrinology with us.

We hope that the abstracts of valuable researchs and case reports which publish in this issue would give the related readers and scientists novel ideas for the future researchs.

Symposium Chairs:

Prof. Dr. Ferda Özkınay
Prof. Dr. Şükran Darcan
Prof. Dr. Füsun Saygılı

EDITORIAL

(P-01)

Late-Onset Congenital Adrenal Hyperplasia Diagnosed at 53 Years of Age

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Our aim was to present a case of late-onset congenital adrenal hyperplasia (LOCAH) diagnosed at 53 years of age because of bilateral surrenal adenoma (BSA).

At 53 years of age, 11 years post-menopausal woman was referred to our out-patient clinic due to BSA. Patient's physical examination was unremarkable and Ferriman-Gallwey score was 4. There was no history of diabetes or hypertension. Adenomatous lesions were detected in the right adrenal gland corpus (10 mm in diameter) and left adrenal gland corpus (20 mm in diameter) demonstrated as out-of-phase sequence signal loss on abdominal magnetic resonance imaging (MRI). There was no significant increase in lesion diameter from previous MRI.

Hormonal function tests for Cushing's syndrome, pheochromocytoma, and Conn's syndrome were negative. The patient have two sons after spontaneous pregnancy. She has no hirsutism. Basal level of 17-hydroxy progesterone (17-OH-P) was 6.53 ng/mL thus 250 mcg adrenocorticotropic hormone stimulation test was ordered. Test results were cortisol 0' = 8 ug/dL, cortisol 30' = 9.16 ug/dL, cortisol 60' = 10.12 ug/dL, 17-OH-P 0' = 11.43 ng/mL, 17-OH-P 30' = 42.85 ng/mL, and 17-OH-P 60' > 50 ng/mL. After the test, LOCAH and adrenal insufficiency were diagnosed. Hydrocortisone (25 mg/day) treatment was started. *CYP21A2* mutation analysis revealed homozygous mutations of p.Arg339His (c.1016 G > A) in the exon 8 and p.Pro453Ser (c.1357 C > T) in the 10th exon. Test for patient's family members was ordered.

Patients followed with BSA should be investigated for LOCAH, even postmenopausal ones.

(P-02)

8Q22.3-Q24.23 Duplication: A Case Report

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We present a rare case of 8q duplication in a patient with oral frenulum history and absence of mental retardation.

A 7-year-old girl was referred to our clinic for hypertrichosis and dysmorphic facial appearance. On physical examination, hypertrichosis, upslanted palpebral fissures, epicanthus, hypertelorism, microretrognathia, high and broad nasal root, distinct glabella, fine upper lip, broad and flat philtrum, and clinodactyly were detected. She had a history of an operation for oral frenulum. Haemogram, routine biochemistry, hormone profiles, karyotype analysis, and brain magnetic resonance imaging (MRI) as well as ophthalmology, otolaryngology, and child psychiatry consultations were requested.

Hemogram, routine biochemistry, hormone profiles, brain MRI results, and the ophthalmologic evaluation were normal. Chronic otitis media was detected on otolaryngologic examination. IQ test score was reported as 95. Chromosome analysis revealed a 46,XX,der(8)add(8)(q24.1) karyotype. Karyotypes of mother, father, and sister were normal. Array comparative genomic hybridization (aCGH) was done to determine where the extra material came from. A duplication of 35.9 Mb at 8q22.3-q24.23 was detected.

Our case had similar phenotypic features to 8q duplication cases, such as hypertrichosis, hypertelorism, microretrognathia, and long philtrum. However, to our knowledge, this is the first case of 8q duplication with oral frenulum and without mental retardation.

(P-03)

Parental View on the Terminology of Disorders of Sex Development

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Disorders of sex development (DSD) is a nomenclature proposed to defeat the discomfort of families and patients. The aim of this study was to investigate the perception and usage of terminology among the parents of DSD patients in our country.

The records of the DSD council between years 2008-2015 were reviewed retrospectively. Parents were contacted through telephone inquiries focusing on the terminology the parents knew and tend to use.

In total, 121 patients were evaluated in monthly meetings of DSD council and 79 inquiries were completed. Median age at diagnosis was 1 year (0-16 years). Forty-one percent of the

patients were diagnosed in the newborn period. Median follow-up was 5 years (1-19 years). Follow-up period was longer than five years in 56%. About half of the families admitted knowing the terms DSD, ambiguous genitalia, indeterminate genitals, and intersex; however, only 2% preferred using DSD, 6% intersex, and 14% ambiguous genitalia. Fifty-two percent of the parents used a disease name in Latin addressing the disorder. Sixty-nine percent who were familiar with the name indeterminate genitals were diagnosed in the neonatal period ($p = 0.046$). The clinic mostly involved in the management was related to referring the disease with a name in Latin ($p = 0.024$) or as chromosomal abnormality ($p = 0.048$).

Parents of DSD patients avoid using any word containing "sex" and prefer disease names in Latin instead. Direct translation and usage of new terminology may not achieve the desired result. Each country has its own social norms, local committees should be employed to develop proper terminology.

(P-05)

A Male Case of Aromatase Deficiency with a Novel *CYP19A1* Mutation

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Aromatase deficiency (AD) is a rare autosomal recessive disorder caused by *CYP19A1* gene mutations and is characterized by lack of conversion of androgens to estrogens. Men usually present with continuing linear growth after puberty, tall stature, unfused epiphyses, delayed bone age, genu valgum, decreased bone mineral density, obesity, dyslipidemia, liver steatosis, insulin resistance, and impaired fertility. We here report a male case of aromatase deficiency with a novel *CYP19A1* mutation.

A 30-year-old man with a tall stature (192 cm) presented with genu valgum. He complained to grow continuously. X-ray revealed incompletely fused epiphyses. Bone age was compatible with 14 years. Follicle-stimulating hormone and luteinizing hormone and testosterone were in normal ranges, but estradiol was undetectable. Insulin resistance as well as elevated serum alanine aminotransferase, aspartate aminotransferase and gamma-glutamyl transferase levels were found. Abdominal ultrasonography revealed steatohepatitis. In bone mineral density analysis, Z score was normal. The sperm count and vitality were normal. Sequencing of the *CYP19A1* gene revealed a novel 6-base homozygote deletion in exon 10 (c.1465_1470del GAAATG). The parents and sister were heterozygous for the same mutation. Estrogen replacement therapy was started.

We report a male patient with AD who had a novel deletion in *CYP19A1* gene. AD is an extremely rare condition. Till recently, all mutations have been in coding exons, mostly in exons 9 and 10. Estrogen replacement in AD has great impact on the recovery of dysplastic bone, lipid, liver, and glucose metabolism, but fails to improve insulin resistance. This will hopefully clarify the link between the deletion and the phenotype.

(P-06)

CYP11A1 Mutations Result in Various Clinical Phenotypes

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Cytochrome P450 side-chain cleavage enzyme (CYP11A1) is the first enzyme and catalyzes the rate-limiting step of steroidogenesis. CYP11A1 deficiency is associated with adrenal insufficiency (AI) and commonly with a disorder of sex development (DSD) in 46,XY individuals. Our objective was to define the clinical presentation of our patients with CYP11A1 mutations, one of whom had a novel CYP11A1 mutation.

Four patients were presented. Case 2 has been reared as a girl and she has a novel CYP11A1 mutation. Cases 3 and 4 are siblings. Clinical findings are given in Table 1.

These cases demonstrate that CYP11A1 deficiency can be seen in the newborn period or in early childhood as classical or non-classical forms. Normal genital appearance can found in 46,XY patients in non-classic form and this does not exclude life-threatening AI risk.

Table 1. Clinical findings

	Case 1	Case 2	Case 3*	Case 4*
Age at diagnosis, year	1.24	0.08	5.16	2.64
Karyotype	XX	XY, t(4;9)(p16.6?;p13.3)	XY	XY
Birthweight, g/gestational weeks	3600/39	1750/33	2200/39	2800/39
Parents	1. cousin	1. cousin	Same region	Same region
Presentation	Adrenal crisis	Adrenal crisis	No symptom	Adrenal crisis
Length/Height, cm (SDS??)	72 (-1.83)	44 (-6.05)	105 (-1.10)	95 (0.96)
Weight, g (SDS??)	8000 (-2.65)	1675 (-4.67)	18.6 (-0.10)	11.5 (-1.55)
External genitalia	Labial synechiae	Normal female	Penis 6x1.8 cm	Penis 5x2 cm
Adrenal imaging	Normal (MRI)	Hyperplasia (MRI)	Normal	Normal
Basal cortisol, µg/dL	< 1	8.15	7.6	9.2
Stimulated cortisol, µg/dL	< 1	8.03	7.8	9.4
Adrenocorticotropic hormone, pg/mL	259	1250	>1250	>1250
Progesterone, (ng/mL, N: < 30)	1.4	0.03	< 0.1	< 0.1
DHEAS, (µg/dL, N: 50-500)	4.2	16.41	48.5	30.7
17-OHP, ng/mL	0.7	0.56	0.34	
1.4 Androstenedione, ng/mL	0.18	1.2	0.33	0.33
Testosterone, (ng/mL)	0.3	0.02	< 0.13	< 0.13
Aldosterone, (ng/mL, N: 35-410)	< 1	33	1.3	0.16
Renin, pg/mL (N: 5.2-33.4) PRA (N:0.98-4.18)	> 500 -	> 520 -	-	- 19.43
CYP11A1 mutation	p.R451W	p.W152X	p.R451W	p.R451W

(P-07)

The Role of Adenovirus Serotype 36 in Childhood Obesity

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This study aimed to determine the role of Adenovirus 36 (Adv 36) in childhood obesity and to evaluate the obesity-triggering effect of its latent infection on adipose tissue.

The study group was composed of 31 obese children who were admitted to the pediatric endocrinology outpatient clinic, while the control group comprised 30 non-obese children without any chronic disease. In obese children, both an adipose tissue sample and blood samples were obtained, while only blood samples were obtained in control subjects. The adipose tissue samples were taken by a needle aspiration procedure from the subcutaneous tissue of abdomen in obese children. Besides biochemical tests, Adv 36 specific antibody and viral DNA in blood samples were investigated in all subjects, while viral nucleic acid with real-time PCR from adipose tissue was investigated only in obese subjects.

SGPT, triglyceride, and insulin levels were higher in the obese group. There was no case with a positive result of Adv 36 antibody in the control group, while the seropositivity rate for Adv 36 was 13% among the obese children. Regarding the latent Adv 36 infection, there was no positive PCR result from the adipose tissue samples in obese children.

There was a high serological evidence of Adv 36 infection in obese individuals. However, the results of PCR in adipose tissue could not show the presence of latent infection among obese children in the current study. Thus, further studies are needed to evaluate the possible associations between Adv 36 and development of childhood obesity.

(P-08)

A Case of Congenital Generalized Lipodystrophy Type 2 with Novel *BSCL2* Gene Mutation

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Congenital generalized lipodystrophy (CGL) is a rare autosomal recessive disorder characterized by generalized absence of adipose tissue, extreme insulin resistance, hypertriglyceridemia, hepatomegaly, hepatic steatosis, and early onset of diabetes. Herein, we described a case with CGL2 due to novel homozygous *BSCL2* gene mutation.

Three years-seven months old girl presented with a general lack of subcutaneous fat, prominent muscular hypertrophy, hollow cheeks, triangular face, acanthosis nigricans in fold areas, especially in the neck-bilateral axilla, hypertrichosis in arms-legs, abdominal swelling due to hepatomegaly, which are characteristic physical findings of CGL. Her parents were first-degree cousins. In laboratory: Glucose 75 mg/dL (70-105), C-peptide 6.8 ng/mL (0.9-4.3), insulin 47.4 µIU/mL (1.9-23), HbA1c 5.2% (4.8-6.0), total cholesterol 132 mg/dL (< 200), and triglyceride 134 mg/dL (< 200). Hyper triglyceridemia was firstly detected at 5 years of age with metformin therapy. Despite taking metformin treatment, the patient's insulin levels increased steadily, and serum AST levels were also elevated. At the age of nine, grade 2 hepatic steatosis with hepatomegaly was detected in ultrasonography.

During follow-up, her HbA1c level has increased to 6.5% at the age of eleven years and three months. The fasting and 2-hour post-OGTT glucose-insulin levels of the patient were 152 mg/dL-158.3 µIU/mL and 209 mg/dL-95.8 µIU/mL, respectively. Insulin detemir was started in addition to metformin treatment because of diagnosis diabetes.

A clinical diagnosis of CGL was corrected by the identification of a novel homozygous mutation (IVS2 + 2 T > C) in the *BSCL2* gene. Analyzes with GenSplicer and Human Splicing Finder modeling programs show that this mutation can cause the disease.

(P-09)

Gene Conversion and Congenital Adrenal Hyperplasia: Two Case Reports

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Congenital adrenal hyperplasia (CAH) is one of the inborn metabolic disorders inherited in an autosomal recessive manner. 95% of CAH cases are due to 21-hydroxylase deficiency. 21-hydroxylase enzyme have an active gene and a pseudogene. The rearrangements between these two genes play an important role in the pathogenesis of CAH. Herein, we present the cases of two siblings with different phenotypes and different chromosomal sex who both have a large gene conversion and a point mutation.

21-hydroxylase gene strip assay and MLPA analysis were performed in the two sibling cases.

The case with male phenotype has been diagnosed with CAH due to salt-wasting crises, macrogenitalia, and hyperpigmentation when he was 1 month old. Karyotype analysis results were 46,XY and SRY(+). The female case with 46,XX has been diagnosed with CAH due to salt-wasting crises and ambiguous genitalia in the newborn period. Results of CAH strip assays were c.89C > T(P30L) (N/M), c.329-336del(Del 8bp E3) (N/M), c.290-13A/C > G (I2 Splice) (M/M) in both cases. In MLPA analysis, heterozygous increase in CYP21A1P-1 (-113 SNP) and CYP21A1-P-3 (del8nt) mutation regions, heterozygous loss in *CYP21A2*-1wt (-113 SNP) and *CYP21A2*-3 wt (del8nt) regions, and homozygous mutations in *CYP21A2*-3 wt (I2 G-C), *CYP21A2*-3 wt (I2G-A) regions were detected. It was thought that the cases have received an allele with heterozygous mutation in c.290-13A/C > G (I2 Splice) region from one parent and a gene converted allele from the other. Mutation analysis was planned for parents.

The cases were presented here in order to emphasize the importance of MLPA analysis when diagnosing CAH.

(P-11)

Heterozygous p.D61G Mutation in a Patient with Noonan Syndrome

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Noonan syndrome is an autosomal dominant disease resulting from mutations in the ras-associated mitogen activating protein kinase pathway involved in signal transduction associated with cell proliferation, differentiation, life, and metabolism.

A girl from non-consanguineous family was referred to pediatric endocrine department because of short stature. The 15-year-old girl was born with weight 2300 g by caesarean section and was followed due to pulmonary valve stenosis and mitral insufficiency in the pediatric cardiology department; she underwent cardiac surgery during the infant period. On physical examination height was 131.6 cm (< 3 p), height SDS -4.73, weight 28.7 kg (< 3 p), weight SDS -5.31, target height 150.65, and target height SDS was 1.95. Physical examination also revealed dysmorphic facial appearance with webbed neck, hypertelorism, epicanthus,

downward palpebral fissures, low-set ears rotated backward, triangular face, micrognathia, high-arched palate, widely spaced nipples, cardiac operation scar, and pectus excavatum. Full blood count, biochemical analysis, and thyroid function tests were found to be normal in terms of short stature.

Since the dysmorphic features were consistent with Noonan syndrome, p.D61G heterozygote mutation in *PTPN11* gene was found. The patient with Noonan syndrome was started treatment with 45 micrograms/kg/dose of growth hormone because of short stature and insufficient height velocity.

In this report, Noonan syndrome patient associated with heterozygous P.D61G mutation was presented. Early diagnosis and appropriate treatment will prevent the development of complications.

(P-12)

A New Mutation in an Infant with Hypercalcemia

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Hypercalcemia is a serious condition, which may threaten life. Familial benign hypocalciuric hypercalcemia (FBHH) is a benign situation which develops due to inactivating mutation of calcium sensing receptor (CaSR). Differential diagnosis of FBHH is important in order to prevent unnecessary laboratory tests and treatments.

A three-month-old infant, who was born 2950 g on 38th gestational week to healthy unrelated parents, was admitted to pediatric endocrinology department due to high TSH levels. Her anthropometric evaluation was appropriate for her age and she did not have any dysmorphic stigmata. She was diagnosed with hypothyroidism and put on LT4 treatment. When she was 5 months old, her serum calcium was 11.34 mg/dL (8.8-10.6).

The patient did not have any clinical symptoms of hypercalcemia. Serum phosphorus, parathormone, vitamin levels, urine calcium/creatinine, urine analysis, and renal ultrasonography were normal. Oral hydration was started and her calcium level decreased to 10.8 mg/dL on follow-up. Biochemical and hormonal parameters of father and mother of the patient were evaluated to determine the etiology of hypercalcemia. Whole exome sequencing was performed to the patient and homozygote mutation on exon 7 (p.Glu1011Gln/c.3031G>C) was detected. In order to determine if the parents of the patient had heterozygote mutation or if this is a *de novo* mutation, genetic analysis was also performed to the parents.

To the best of our knowledge, the mutation found in our patient was not mentioned in the literature before. We think that this mutation may cause FBHH in our case. Functional evaluation should be performed for definitive diagnosis.

(P-13)

An Infant with Leydig Cell Hypoplasia Presenting with Bilateral Inguinal Masses

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Luteinizing hormone/chorionic gonadotropin receptor *(LHCGR)* is essential for normal male sex differentiation. Inactivating mutations of *LHCGR* gene result in varying degree of Leydig cell hypoplasia (LCH) that causes 46,XY DSD.

A 2-year and 1-month-old female infant was referred to us for further evaluation of DSD. She was the fourth child of healthy consanguineous Turkish parents and was born at 38 weeks. The patient was raised as female. Her mother noticed bilateral masses on her inguinal areas and brought her to the local hospital. The abdomen USG revealed bilateral masses (possibly testicular structures) on both inguinal region. On admission, her weight was 0.95 SDS, height was 3.4 SDS, and physical examination was normal except for the palpable gonads in both inguinal regions. Her external genitalia was completely female in appearance.

Hormonal investigations showed low testosterone (13.6 ng/mL) with high gonadotropin (follicle-stimulating hormone = 6.1 IU/L and LH = 12.53 IU/L) and AMH (>23 ng/mL) levels. Serum levels of 17-OHP, DHEAS, and AS were within normal ranges. Testosterone response to 3-day HCG stimulation test was absent (sT = 14.47 ng/dL). The karyotype was 46,XY. Pelvic ultrasound revealed absent uterus and ovaries but presence of testicular structures in the superior inguinal canal bilaterally. Bone age was 2 years. The diagnosis of LCH was considered in the patient. *LHCGR* gene sequencing demonstrated a homozygous c.1435C>T (p.R479*) mutation that confirmed the diagnosis. In the parents genetic analysis is being done.

Although LHC is usually diagnosed at pubertal or postpubertal period, this case demonstrates that LCH can be seen in infancy period presenting with inguinal masses.

(P-14)

A Case Presentation: Sleeve Gastrectomy with Transit Bipartition as a Treatment of Type 2 Diabetes Mellitus Applied for the First Time to a Bulgarian Citizen

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Sleeve gastrectomy (SG) with transit bipartition (TB) was applied to a Bulgarian patient for the first time and no other case presentation was found in the literature using this treatment method in Bulgaria. Our aim is to introduce and disseminate this procedure in our country for the treatment of patients with type 2 diabetes mellitus (T2DM).

A 40-year-old gentlemen, height 176 cm, weight 115 kg (BMI: 37.2 kg/m^2), presented with a 3-year history of T2DM. His grandmother has T2DM. First, he was admitted in a hospital in Sofia. His Hba1C level was 9.31 % and blood glucose was 16 mmol/L. He was on treatment with metformin 850 mg morning and evening 2 times daily. Patient complaints were polyuria, polyphagia, weakness, and headache. He was informed about metabolic surgery and he referred to the clinic in Istanbul willingly to have a surgical operation.

In May 2016, he underwent laparoscopic SG with TB in İstanbul. The patient recovery was successful, and 16 kg weight loss was observed in 4 months. Hba1C value was observed in normal range -6 %. He is not on any drug treatment for his T2DM.

Surgical treatment options for diabetes mellitus are available nowadays to treat patients with obesity. The ABCD score, which comprise age, BMI, C-peptide level, and duration of T2DM (years) was reported as useful in predicting the success of T2DM treatment using metabolic surgery. SG with TB operations are getting more popular, but in our country, this is the first case of a patient treated with SG + TB.SG + TB is a simple procedure that results in rapid weight loss and remission or major improvement of comorbidities. As a conclusion of this case report, TB is an excellent complement to SG.

(P-15)

Incidentally Detected Monogenic Diabetes Case

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We present our case to emphasize that monogenic diabetes should be considered in young patients having positive family history and whom diabetes could not be classified.

A 25-year-old female was referred to our clinic due to elevated blood glucose. The patient had no symptoms of hyperglycemia. She had no chronic illness and did not take any medication. Her 55-year-old mother has been followed for uncomplicated diabetes for 16 years with oral antidiabetics, and her 75-year-old grandmother had uncomplicated diabetes for 30 years treated with basal insulin. On physical examination, vital signs were stable, height 168 cm, body weight 70 kg, BMI 24.8 kg/m^2. Systemic examination was normal, and no findings of insulin resistance were present.

Laboratory findings revealed that fasting plasma glucose (FPG) was 140 mg/dL, postprandial plasma glucose 178 mg/dL, and HbA1C 7.2 %. Blood count and biochemical parameters were normal. Fasting C-peptide was 2.32 ng/mL, urine ketone negative, anti-GAD, ICA, and anti-insulin antibodies were negative. We recommended life-style modifications and metformin treatment. Then, considering the patient age, family history of diabetes, absence of insulin resistance, negative autoantibodies, and normal body mass index, we performed genetic analysis for maturity-onset diabetes of the young (MODY). Heterozygous mutation of p.R191W (c.571C > T) was detected in glucokinase gene, and diagnosis of MODY type 2 was confirmed. She was followed with life-style modifications without metformin. FPG and glucose tolerance test results of siblings of the patient were normal. Genetic screening was recommended for the family.

It may be difficult to determine the type of diabetes in young patients. In suspected cases, genetic analysis may help to establish the definite diagnosis of MODY.

(P-16)

A Rare Cause of Insulin-Dependent Diabetes: Two Siblings with Walcott-Rallison Syndrome

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Wolcott-Rallison syndrome (WRS) is a rare autosomal recessive disorder characterized by neonatal or early infancy onset insulin-dependent diabetes and epiphyseal dysplasia. Other frequent multisystem manifestations include recurrent hepatitis, renal dysfunction, failure to thrive, developmental delay, neutropenia, and hypothyroidism. Herein, we reported two siblings with WRS.

Case 1: A 14-month-old male infant was brought to the hospital for feeding difficulty and vomiting and was diagnosed as diabetic ketoacidosis. He developed liver and renal failure after admission and was managed appropriately. Later on, physical examination showed growth failure and skeletal abnormalities, as well as dysmorphic features. Because of accompanying diabetes and skeletal abnormalities, WRS was suspected and the diagnosis was confirmed by genetic analysis which revealed a homozygous

partial gene deletion, c.1886 (c.2817+1_c.2818-1)del on the *EIF2AK3* gene. The patient's parents were both heterozygous for this mutation and are therefore carriers of WRS.

Case 2: The three-month-old sister of the first case was diagnosed as diabetes. Because of her family history, the diagnosis was confirmed with genetic testing which revealed the same partial gene deletion as in her brother.

Hepatic and renal dysfunctions are typical features of this syndrome. Our first patient presented with typical symptoms and signs of WRS. Although case 2 does not have the typical signs of the syndrome, it may develop later. Children with WRS usually present in the first few months of life with diabetes, and it is recommended that any child presenting with diabetes within the first 2 years of life should be tested for EIF2AK3 mutations.

(P-17)

Isolated Hypoaldosteronism: A Case Report

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Isolated hypoaldosteronism (IHA) is a rare (1/1.000.000) AR disorder caused by mutations in *CYP11B2* gene and may result in life-threatening salt wasting and failure to thrive an. We presented this case because of the rareness of disease and our patient is only the second Turkish case with a genetically confirmed diagnosis.

A 3-day-old male first presented with jaundice and physical examination with normal findings. The parents are Turkish and consanguineous. Initial laboratory examinations showed hyponatremia (129 mEq/L) and hyperkalemia (6.9 mEq/L). Endocrinological evaluation showed low plasma aldosterone concentration of 40 pg/mL (50-900 pg/mL) and markedly elevated plasma renin activity (PRA) >200 ng/mL/hr (2.35-370 ng/mL/hr); cortisol level after adrenocorticotropic hormone stimulation was 31.5 ug/dL. He was started a fludrocortisone treatment as 0.1 mg/daily with IHA diagnosed. Fludrocortisone dose was raised to 0.4 mg/daily. At the age of 3 years, hypertension was detected while his electrolyte levels were normal. His treatment was discontinued. At the eighth day without treatment, aldosterone was 10 pg/mL (50-900 pg/mL), PRA >10 ng/mL/hr (1-6.5 ng/mL/hr), corticosterone 1.5 ng/mL (0-3.5 ng/mL), 18-OH corticosterone 15 ng/dL (6-85 ng/dL), 18-OH corticosterone/aldosterone 15 (2.4-10.5), Na, 132 mmol/L, and K 5 mmol/L.

Genetic sequencing identified that the proband has homozygous p.I236N mutation in *CYP11B2* gene and his parents were both heterozygous. Despite this mutation was not reported in any database, another Turkish family was reported with same clinical features recently. PolyPhen-2, SIFT, and MutationTaster indicated this mutation as harmful.

Although there is no functional study of the reported p.I263N mutation which is assumed to be the cause of the disease, we present this case because two independent families were reported with the same clinical features and the mutation was predicted to be harmful by *in silico* methods.

(P-18)

Evaluation of the Response to the First Two Years of Growth Hormone Treatment in Kabuki Make-Up Syndrome

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The Kabuki make-up syndrome (KMS) is characterized by mental retardation, typical facial appearance, skeletal anomalies, joint laxity, and post-natal growth deficiency. There are limited publications on growth hormone therapy in KMS. Our aim is to present the response to growth hormone (GH) treatment in two KMS patients with GH deficiency in the first two years.

Case 1: A girl with KMS who started treatment for GH at 11.4 years old had a height of 128.6, 138.8, and 146.9 cm, a height SDS of -2.98, -2.6, and -2.01, a growth velocity of 3.2, 9.9, and 8.4 cm/year, and growth velocity SDS of -3.41, +4.14, and +3.13 at pretreatment, one-year, and two-year follow-up on treatment, respectively.

Case 2: The second case whose GH treatment was started at the age of 5.2 years had height of 94.8, 102.2, and 109.2 cm, height SDS of -3.31, -2.96, and -2.54, growth velocity of 4, 7.4, and 7 cm/year, and growth velocity SDS of -2.3, +1.6, and +1.09 at pretreatment, one-year, and two-year follow-up with treatment, respectively.

In our cases, a good response to GH treatment was obtained as in the few patients in the literature.

The post-natal growth retardation seen in 100% of patients with KMS can be accompanied by lack of GH.

(P-19)

A Novel Mutation in a Patient with 5-α Reductase Deficiency Reared as Girl

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5-α reductase deficiency is one of 46,XY disorders of sexual differentiation characterized by androgen metabolism disorder. In the literature, there are few cases with 5-α reductase deficiency reared as girl.

A 12-year and 8-month-old female patient presented with primary amenorrhea, absent breast development, axillary and pubic hair. Physical examination revealed a weight of 53.9 kg [75-90p, 0.87 standard deviation score (SDS)], a height of 167 cm (95p, 1.72 SDS), and normal vital signs. Genital examination disclosed female external genitalia with no cliteromegaly, hirsutism, or acne. The target height was 160.2 cm, and bone age revealed 12 years.

Follicle-stimulating hormone, luteinizing hormone, estradiol, and total testosterone levels were 3.68 mIU/mL, 3.04 mIU/mL, < 10 pg/mL, and 202.76 ng/mL. Adrenocorticotropic hormone and serum cortisol levels were normal in terms of adrenal insufficiency. Ultrasound imaging revealed no uterus and ovary. Karyotype analysis revealed 46,XY and SRY + was detected by quantitative fluorescent polymerase chain reaction. 5-α reductase deficiency was diagnosed with homozygous IVS3 + 1G > T (c.547 + 1G > T) mutation. Prophylactic bilateral gonadectomy was planned.

We emphasize the importance of karyotype analysis in patients with delayed puberty and primary amenorrhea. Prophylactic bilateral gonadectomy should be kept in mind for 5-α reductase deficiency in patients reared as girl to prevent the development of gonadal malignancy.

(P-20)

Two Cases of Klinefelter Syndrome

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Klinefelter syndrome is the most commonly seen sex chromosomal disorder in males. The typical clinical features of this syndrome are symptoms of hypogonadism in different degrees. Up to 80% of patients with Klinefelter syndrome have 47,XXY karyotype, which is the prevalent type.

Case 1: A 36-year-old male patient applied to our clinic due to the complaint of erectile dysfunction. On physical examination, height was 183 cm, weight 80 kg, and BMI was 23.9 kg/m^2. Axillary and pubic hair were present. He had bilateral gynecomastia. Testis volume measured with orchidometer was 20 mL. Karyotype was 47,XXY. In the laboratory examination, follicle-stimulating hormone was 36 mIU/mL (1.27-19.26), luteinizing hormone (LH) 25 mIU/mL (1.24-8.62), and total testosterone was 2.15 ng/mL (2.8-8). Spermiogram demonstrated azoospermia. Intramuscular testosterone treatment was initiated once in three weeks.

Case 2: A 43-year-old male patient applied to our clinic due to the complaints of libido loss and infertility. On physical examination, height was 185, weight was 95 kg, BMI was 27.8 kg/m^2, axillary and pubic hair were present, the penis was small, and he had truncal obesity. Karyotype was 47,XXY. Follicle-stimulating hormone was 61 mIU/mL (1.27-19.26), LH 25 mIU/mL (1.24-8.62), total testosterone 0.24 ng/mL (2.8-8), and free testosterone was 3.15 pg/mL (57-178). In bone densitometry, L1-4 Z was -3.5. Intramuscular testosterone treatment was initiated once in three weeks.

In Klinefelter syndrome, testosterone replacement treatment eliminates all negative effects related to androgen deficiency; however, it has no effect on fertility. It should be remembered that Klinefelter syndrome may be detected in infertile males.

(P-21)

Major Depression and Fabry Disease: A Case Report

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Fabry disease is a genetic lysosomal storage disease which affects several organs. The main defect is absence of alpha galactosidase enzyme activity. Kidney, central nervous system, cardiovascular system, and ocular system are the main influenced systems, but neuropsychiatric symptoms may develop in some cases. Current studies showed that psychiatric symptoms may be seen in both genders apart from neurological ones.

A 22-year-old female patient with history of two suicide attempts was consulted from psychiatry clinic. Her father had Fabry disease. He had renal transplantation and his enzyme level is low 3.2 nmol/mg/h (normal range > 30). GLA gene mutation analysis revealed that he had p.G261D (c.782G > A) heterozygote mutation. Enzyme replacement treatment was administered

(agalsidase alfa). His daughter had flushing in her face and she could not sweat. Plenty angiokeratoma were found on her body. Eye examination was normal and there was no cardiac pathology. The same mutation was detected. Enzyme replacement therapy has been started.

Despite the fact that Fabry disease is an X-linked disorder, several female heterozygote mutation carriers have distinct clinical symptoms. Our patient does not have any major characteristics of Fabry disease, but she presented with major depression and angiokeratoma besides she had heterozygote mutation. In the literature, few mutation cases especially in men were associated with depression; however, no data found for women. It is well-known that mutation and phenotype relation is very important to predict the prognosis of the illness. It should be kept in mind that heterozygote mutation of p.G261D (c.782G > A) may be related with depression with female patients.

(P-22)

A Case of MEN 2A: D631Y Mutation

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Multiple endocrine neoplasia 2A (MEN 2A) is a hereditary disease comprising medullary thyroid carcinoma (MTC) (95%), pheochromocytoma (50%), parathyroid hyperplasia or adenoma (15-30%). RET mutations are seen generally in exon 10. Exon 11, 631 codon mutations are not common in MEN.

A 29-year-old male patient applied to our clinic. His mother was operated and diagnosed with MTC. Heterozygous D631Y RET mutation was detected in his mother. After this result, our patient was evaluated for RET mutation and MEN. Calcitonin value of the patient was normal and no nodule was detected on thyroid ultrasound. RET oncogene was positive for our patient as D631Y mutation. For the screening of MEN components, twenty-four hour urinary metanephrine and normetanephrine were high. Magnetic resonance imaging revealed adrenal adenoma 29x27x31 mm in diameter at the left adrenal. The patient underwent an operation in 2014 and pathology was consistent with pheochromocytoma. Prophylactic thyroidectomy was recommended, however, the patient did not accept this. He has been followed for development of thyroid nodule and evaluation of calcitonin level. At last visit, laboratory examination revealed PTH of 31.3 pg/mL (15-65), Ca 10.2 mg/dL (8.6-10.2), TSH 3.98 µIU/mL (0.35-5.50), fT_4 1.47 ng/dL (0.89-1.76), calcitonin 5.77 pg/mL (0-10), and 24-hour urinary metanephrine and normetanephrine were normal.

RET 631 codon mutation is seen rarely in MEN patients. This genetic profile might be related to the less vigorous clinical disease behavior and the late onset of MTC.

Pheochromocytoma might be the first manifestation prior to the development of MTC.

(P-23)

A Case of Androgen Insensitivity Syndrome Presenting with Micropenis

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The patients with androgen insensitivity syndrome can present with various phenotypic anomalies having as a common aspect the loss of reproductive characteristics.

A boy from non-consanguineous family was admitted to pediatric endocrine department because of micropenis. A 7-year and 8-month-old boy was born with 3650 g by caesarean section. On physical examination, height was 124.1 cm (25-50p), height SDS -0.27, weight 29.7 kg (75-90p), and weight SDS was 1.09. The patient was conscious, oriented, and well-nourished with normal secondary sexual characteristics for his age. Genital examination revealed a stretched penile length of 3 cm, penile width of 0.5 cm, and no axillary and pubic hair. Right and left testis were palpated in the scrotal sac.

Karyotyping revealed a normal 46,XY karyotype. Serum follicle-stimulating hormone, luteinizing hormone, and total testosterone levels were 0.79 mIU/mL (normal reference range < 6.7), 0.06 mIU/mL (normal reference range 0.3-6.0), and 4.80 ng/dL (normal reference range < 7), respectively. Serum testosterone level was increased in response to 1500 units/dose HCG stimulation test for 3 days. No mutation was found for 5-α reductase deficiency. Androgen insensitivity syndrome was diagnosed with hemizygote p.L863F (c.2587C > T) mutation.

We emphasize the importance of genetic analysis in patients with micropenis. Routine genetic analysis to confirm androgen insensitivity syndrome may predict the long-term prognosis and management.

(P-24)

Two Siblings with Microcephalic Osteodysplastic Primordial Dwarfism Type II (MOPD II)

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We aimed to identify the genetic cause of severe short stature and microcephaly in two siblings.

A ten-year-old boy presented with short stature. He was born with a birth weight of 1300 grams (-2.7 SDS) at 34 weeks of gestational age. On physical examination, height was 86 cm (-8.9 SDS), weight 8.4 kg (-7.9 SDS), BMI 11.4 kg/m^2 (-5.6 SDS), and head circumference was 37.7 cm (-9.1 SDS). Development was delayed. He started walking at 3 years, speaking with single words at 2 years, and he cannot make sentences yet. He had prominent nose, microcephaly, micrognathia, and microdontia. There were areas of hypo- and hyperpigmentation, cutis marmorata, and few cafe au lait spots on skin. Parents were first-degree cousins. Height of father was 177.5 cm (0.2 SDS) and height of mother was 159 cm (-0.7 SDS); target height was 161.8 cm (-0.2 SDS). His sister presented at 9 months of age and her height was 50.1 cm (-7.1 SDS), weight 3.8 kg (-6.3 SDS), and head circumference was 33.5 cm (-8.1 SDS). She was born with a birth weight of 1135 grams (-2.5 SDS) at 33 weeks of gestational age. Routine laboratory tests, serum levels of free triiodothyronine, free thyroxine, thyroid-stimulating hormone, insulin-like growth factor 1, and insulin-like growth factor binding protein 3 were normal.

Genetic analysis showed homozygous pericentrin mutation c.3109G > T, p.Glu1037 in both siblings. Parents were heterozygous for this mutation.

MPOD II is characterized by severe intrauterine and postnatal growth retardation, microcephaly, and distinctive face; patients with this disorder should be screened for cerebrovascular abnormalities.

(P-25)

A Rare Genodermatosis: H Syndrome

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H syndrome (OMIM # 602782), first described in 2008, is a rare autosomal recessive genodermatosis which is multisystemic and is primarily characterized by cutaneous hyperpigmentation, hypertrichosis, hepatosplenomegaly, hearing loss, heart anomalies, hypogonadism, short stature, hyperglycemia (insulin-dependent diabetes mellitus), and hallux valgus/flexion contractures. It is caused by mutations in the solute carrier family 29 *(SLC29A3)* gene. A 23-year-old female patient who had the characteristic clinical features of H syndrome was referred to our medical genetics outpatient clinic to confirm the clinical diagnosis through molecular testing, to arrange the clinical follow-up and treatment support programme, and to provide the patient with suitable genetic counselling.

Clinical examination was performed. Related tests and imaging methods were planned. All coding exons of *SLC29A3* gene were sequenced.

Physical examination revealed cutaneous hyperpigmentation on the body/on lower and upper extremity skin except knees and elbows, bilateral hypertrichosis on lower extremity (proximal), hepatosplenomegaly (splenomegaly), bilateral sensorineural hearing loss, heart anomalies, hyperglycemia (insulin-dependent diabetes mellitus), hallux valgus/flexion contractures (flexion contractures on bilateral hands/feet). Homozygote nonsense mutation causing premature stop codon (p.Y428*) in *SLC29A3* gene exon sequencing was detected.

H syndrome is a rare genetic disease which requires multidisciplinary treatment because of its multisystemic involvement. Molecular genetic testing is important to confirm the diagnosis, to provide appropriate genetic counselling and to estimate prenatal diagnosis possibilities for the following pregnancies. As far as we are concerned, there are two more cases reported except ours in Turkey until now. More than 100 patients and 20 mutations in *SLC29A3* gene have been described in the world. We find it convenient to present this rarely observed case in order to discuss the clinical findings and the mutation found in our case.

(P-27)

Non-Genetic Factors Altering Birth and Fertility Rates

Dilara Çelebi

Bahçeci BIH IVF Center

The purpose of this project was to understand how Bosnian war affected the fertility and birth rates.

I selected two countries, namely Bosnia and Herzegovina and Turkey and researched and analyzed the results of the national statistical institute of the countries.

Turkey has a higher BMI score for females compared to Bosnia and Herzegovina, but the difference is only 1.9 points in BMI scores. Both countries fall into the average weight category in the index which is above underweight and above overweight and obese category. Total fertility rates of Turkey and Bosnia and Herzegovina show that Turkey has 0.86 higher fertility rates in average when compared with Bosnia and Herzegovina from year 2011 to 2014.

The lower fertility rates may be due to the negative agents on the adults but also post-war trauma on Bosnians. The pronounced reduction in fertility can be linked to particular circumstances in Bosnia and Herzegovina following the war and subsequent economic stagnation and instability accompanying changes in societal behavior.

(P-28)

A Rare Cause of Obesity: ROHHAD Syndrome

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ROHHAD syndrome is a rare syndrome with rapid-onset obesity (RO), hypoventilation (H), hypothalamic (H), and autonomic dysfunction (AD). Rapid weight gain usually begins after the age of 2-3, while hypoventilation occurs in more advanced age. We report the case of a patient who developed hypoventilation at very early age and subsequently obesity, and was diagnosed at the age of 1.5 years.

A male patient developed progressive neurologic deterioration and epilepsy following hypoxic encephalopathy due to sudden respiratory arrest at five months old. At the age of 1.5, he was evaluated for sudden-onset obesity which occurred in the last few months. He received treatment for constipation as well as epilepsy. The weight was 15 kg (+1.4 SD), height 82 cm (-1.0 SD), and BMI 22.3 kg/m^2 (+3.1 SD). Spontaneous breath rate and heart rate were varying between 6-10/min and 45-55/min, respectively. The patient was spastic quadriplegic and had no pupillary reflex. Brain MRI revealed cortical and white matter atrophy. Laboratory values were as follows: serum Na 150 mEq/L, serum osmolality 310 mOsm/kg and urine osmolality 101 mOsm/kg, serum adrenocorticotropic hormone <5 pg/mL, and cortisol 1.01 µg/dL. Other pituitary functions were normal. Treatment with desmopressin and hydrocortisone was initiated for central diabetes insipidus and adrenal insufficiency. All the findings (obesity, pituitary hormone deficiencies, hypoventilation, bradycardia, absence of pupillary reflex, constipation) indicated diagnosis of ROHHAD syndrome.

ROHHAD syndrome should be kept in mind in children with rapid-onset obesity and pituitary hormone deficiencies. These children should be monitored in terms of accompanying findings such as hypoventilation and autonomic dysfunction.

(P-29)

Osteogenesis Imperfecta: Case Report

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Osteogenesis imperfecta is a genetic disorder characterized by osteoporosis, recurrent bone fractures and, consequently, deformities. In many cases, it is chiefly caused by a dominant mutation in the *COL1A1* or *COL1A2* genes that encode type I procollagen.

The medical history of our 41-year-old female patient revealed an earlier diagnosis of osteogenesis imperfecta and 4 fractures. She was diagnosed with the disease in her childhood. She was treated with zoledronic acid twice, once per year. In the clinical examination, she reported that she had no new fractures and her pain reduced after zoledronic acid treatment. Blue sclera was present in her physical examination .The laboratory results were as follows: AST 20 U/L, ALT 22 U/L, ALP 81, Ca 8.8 mg/dL, P 3.0 mg/dL, 25 OH vitamin D 35 ng/mL, TSH 0.995 µIU/mL, fT_4 1.26 ng/dL, and PTH 40.81 pg/mL. Before zoledronic acid treatment, DEXA lumbar total T score was -2.9 and Z score was -2.7. One year after the second zoledronic acid administration, DEXA lumbar total T score was -2.5 and Z score was -2.2. The patient was treated with zoledronic acid for the third time by our team.

The target of the treatment of the cases with osteogenesis imperfecta is to reduce the fractures and pain and to prevent long-term bone deformities thus improve the patient's functional capacity and mobilization. Recently, no new bone fractures have been observed in our patient treated with zoledronic acid. Bearing drug compliance in mind, zoledronic acid could be an alternative to bisphosphonate treatment for suitable patients with osteogenesis.

(P-30)

A Case of 46,XX DSD Due to a Novel Mutation in P450 Oxidoreductase Gene

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P450 oxidoreductase *(POR)* enzyme deficiency is a rare form of congenital adrenal hyperplasia, characterized by combined and partial impairments in steroidogenic enzymes. It may be associated with Antley-Bixler syndrome.

Here we report a newborn with ambiguous genitalia, skeletal malformations, and adrenal insufficiency who was diagnosed with Antley-Bixler syndrome.

A 12-day-old newborn presented with ambiguous genitalia. She was born small for gestation age with a birth weight of 2 400 g at 38 weeks of gestation to a non-consanguineous couple. The pregnancy was uneventful except for maternal voice deepening. Her weight was 2 350 g (-1.99 SDS), her length was 49 cm (-0.12 SDS), and head circumference was 32.5 cm

(-1.47 SDS). She had prominent eyeballs, frontal bossing, dysplastic ears, bilateral upper extremity contractures, left choanal stenosis, and genital virilization (Prader stage 3) with 1 cm phallus and bilaterally non-palpable gonads.

Adrenocorticotropic hormone test showed adrenal insufficiency with a low cortisol peak (6 mcg/dL) and high 17-OH progesterone peak (50 ng/mL). Her karyotype was 46,XX. Bilateral ovarian cysts were detected on ultrasound imaging. These findings suggested *POR* deficiency and Antley-Bixler syndrome. The molecular genetic analysis of *POR* gene revealed a novel compound heterozygous mutation (IVS3-1 G > A (c.238-1 G > A)/ c.929_937delTCTCGGACT). Both parents were heterozygous for these mutations.

POR deficiency should be considered in patients with congenital adrenal hyperplasia with a history of maternal virilization during pregnancy and these patients should be evaluated for the presence of skeletal malformations.

(P-31)

New Chromosomal ins(6;7)(Q13:P22) Anomaly in Klinefelter Syndrome Detected Coincidentally in Patient with Signs of Primary Hypogonadism

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We described our case to show that different genetic disorders can accompany Klinefelter syndrome.

An 18-year-old male patient referred to our clinic with complaints of aggressive behavior, learning difficulties, inability to gain weight, tall stature, lack of facial hair, and erectile dysfunction. He has been using valproic acid for epilepsy. On physical examination, the height was 187 cm, body weight 73.4 kg, BMI 21 kg/m^2, arm span 192 cm, upper body 91 cm, lower body 96 cm, and ratio of pubis-vertex/pubis-floor was < 1. Vital signs were normal, but he had slight mental retardation. Testes were small and in the scrotum; penis length was 2.5cm. No beard was present; axillary and pubic hairs were scarce. Gynecomastia was absent. Systemic examination was normal except for midsystolic murmur. Height of mother and father were 162 and 175 cm, respectively. With these clinical findings, pre-diagnosis of hypogonadism was established and workup was performed.

Blood count and biochemical analysis were normal; follicle-stimulating hormone was measured as 55.95 mIU/mL, luteinizing hormone 8.64 mIU/mL, total testosterone 2.42 ng/mL, and IGF-1 436 ng/mL. Scrotal sonography showed small right (15*10 mm) and left (15*15) testes. Karyotype analysis demonstrated an extra X chromosome (47,XXY) and ins(6;7)(q13:p22). By sequence analysis of exon 1 region of androgen receptor, we detected 22 CAG repeat (normally, 12-30). We diagnosed the patient as having Klinefelter syndrome. Echocardiography performed for chest pain revealed mitral valve prolapse. The patient was informed about genetic counselling and fertility. Testosterone was given for treatment of secondary sexual characteristics.

To our knowledge, our case is the first Klinefelter patient having ins(6;7)(q13:p22); however, its clinical implication is not precise yet.

(P-32)

PROP1-Related Combined Pituitary Hormone Deficiency: Case Report

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Mutations of *PROP1* are the most frequent genetic defect in non-syndromic combined pituitary hormone insufficiency and are characterized by growth hormone (GH), prolactin, TSH, and gonadotropin deficiency.

A 3-year-and-3-month-old girl was referred with growth retardation and abnormal thyroid function tests. She was born

full-term weighing 3200 g and had no significant medical or family history. Body weight was 10.9 kg (-2.54 SDS), height 80.4 cm (-3.38 SDS), and head circumference was 48.3 cm (-0.57 SDS). Systemic examination was normal and her pubertal development was consistent with Tanner stage 1.

The laboratory workup showed TSH 1.99 µIU/mL (0.4-5.0 µIU/mL), fT_3 2.66 pg/mL (1.57-4.71 pg/mL), fT_4 0.62 ng/dL (0.8-1.9 ng/dL), and cortisol 6.42 µg/dL (5-25 µg/dL). Celiac antibodies were negative. Pituitary MRI was reported to be normal. L-thyroxine therapy was started with the diagnosis of central hypothyroidism. While euthyroid, the stimulation tests showed insufficient GH response and normal cortisol response thus GH therapy was initiated. At the age of 12 years and 6 months (bone age 12 years), serum prolactin, follicle-stimulating hormone, and luteinizing hormone (LH) levels were found to be 2.15 ng/mL (3.8-26.7 ng/mL), 0.31 mIU/L, and 0.27 mIU/L. Results of LHRH test was consistent with hypogonadotropic hypogonadism (peak LH 0.4 mIU/L) and estrogen therapy was started. Low-dose adrenocorticotropic hormone test was performed because of low basal cortisol. Cortisol response was insufficient and hydrocortisone treatment was added with the diagnosis of central adrenal insufficiency. Repeated MRI showed a pituitary length of 4 mm. *PROP1* analysis revealed a previously reported, homozygous c.301_302delAG (p.Leu102Cysfs*8) mutation.

Mutations of the *PROP1* primarily affects thyrotroph, lactotroph, gonadotroph, and somatotroph cells. Adrenocorticotropic hormone deficiency is variable. Genetic analysis is important for identification of etiology.

(P-33)

Schmid Type of Metaphyseal Chondrodysplasia with COL10A1 Mutation

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The Schmid type of metaphyseal chondrodysplasia (MCDS) is characterized by short stature, widened growth plates, and bowing of the long bones, resulting from autosomal dominant mutations of COL10A1.

We report a patient with MCDS and COL10A1 mutation.

A 4-year 7-month-old boy was referred to our hospital because of bowing of the legs and short stature. His mother showed short stature and bowing of the legs, too. His height and weight were 75 cm (< 3th p) (-2 SDS) and 21.6 kg (75-90th p), respectively. Ca, P, ALP, PTH, and 25-OH D levels were normal. Radiographs showed findings compatible with MCDS. p.W651*(c.1952G > A) (heterozygote) mutation in the *COL10A1* gene was identified. The patient was diagnosed with MCDS.

We report this patient with MCDS and COL10A1 mutation as it is a rarely seen case.

(P-34)

A Case Report of Seckel Syndrome

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Seckel syndrome is an inherited autosomal recessive disorder characterized by short stature, microcephaly, prominent nose, and typical facial appearance. DNA damages can be detected in different genes, mainly in 3rd and 18th chromosomes. By means of its genetic heterogeneity and easily detectable morphological features, clinical diagnosis can usually be made.

A 19-year-old female patient was diagnosed with Seckel syndrome in pediatric clinic due to typical features of this syndrome at the age of 15. The patient, who already had type 1 DM, applied to our clinic in order to be followed.

On physical examination, prominent nose, flat forehead, micrognathia, high-arched palate, triangular narrow face, and large pinnae were present. On physical examination, height was 136 cm, weight 40 kg, and BMI was 21.63 kg/m^2. Clinodactyly, nail dystrophy, and mental retardation were detected. On cardiac examination, systolic ejection pulse on pulmonary focus was detected. There was no narrative of consanguineous marriage. Her treatment was metformin 500 mg 2x1, pioglitazone 15 mg 2x1, lispro insulin 3x9 units, and glargine insulin 16 units. Her menstrual period was regular. In laboratory examination, FBG was 101 mg/dL, HbA1c was 8.6%, B12 was 176 pg/mL (197-866), hypophyseal hormones were normal. Euthyroid Hashimoto thyroiditis was present. In echocardiography, ASD secundum 6-7 mm was detected. Vitamin B12 replacement was started; pioglitazone was stopped while the doses of insulin were increased. Last value of HbA1c was 6.6%.

Owing to its genetic heterogeneity, molecular prenatal diagnosis is difficult. Involvements may occur in endocrine, cardiac, gastrointestinal, and hematological systems.

(P-35)

Monogenic Diabetes Case Presented with Symptomatic Hyperglycemia and Atypical Mutation

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We report this case to emphasize that appropriate genetic analysis for MODY should be done in young diabetics not coinciding with type 1 or 2 diabetes.

An 18-year-old female patient referred to our clinic with symptoms of dry mouth, polyuria, polydipsia, fatigue, and weight loss (decrease from 58 kg to 51 kg in one month). No chronic diseases or continuous drug usage were noted; her mother had type 2 diabetes. On physical examination, vital signs were stable and systemic examination was normal. In laboratory results, FPG was 261 mg/dL, HbA1C 9.58%, C-peptide 0.9 ng/mL, urine ketone and glucose were positive, blood count and biochemical parameters were normal.

As regards to patient age and clinical findings, pre-diagnosis of type1 diabetes mellitus was established. We started aspart insulin 3x8 unit and detemir insulin 1x12 unit by monitoring blood glucose; then blood glucose stabilized. Anti-GAD and anti-insulin antibodies measured for diagnosis were negative. Due to absence of autoantibodies and positive family history of diabetes, we performed genetic analysis for maturity-onset diabetes of the young (MODY). Compound heterozygous mutation of Ile27Leu/Ser487Asn in *hepatocyte nuclear factor 1α (HNF-1α)* gene was detected and diagnosis of MODY3 was made.

MODY3 revealed by *HNF-1α* defect is the most frequently seen MODY type and composes 50-65% of all MODY cases. Many different mutations were defined in *HNF-1α* gene and clinical findings may differ according to detected mutation. To our knowledge, for the first time in the literature, compound heterozygous mutation of Ile27Leu/Ser487Asn in *HNF-1α* gene was detected in our case. The mutation possibly had contributed to the aggressive clinical pattern in our patient.

(P-36)

Case Report of Leri-Weill Dyscontrosteosis Caused By *SHOX* Gene Deletion

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Short stature is one of the most frequent causes of referral to the children's endocrine outpatient cinics. Short stature affects 2-3% of the general population. The short stature homeobox *(SHOX)* gene is located in the pseudo-autosomal regions of the short arms of the X and Y chromosomes. Deletions or mutations on the gene cause Turner's syndrome, idiopathic short stature, and Leri-Weill dyschondrosteosis (LWD). Here, we present a case with *SHOX* gene deletion detected in a genetic study that was performed due to LWD findings.

A 4-year 3-month-old girl presented to our clinic because of shortness. There was no family history. Her arms were short and curved.

Height was 96 cm (3-10p/-1.47 SDS), body weight 15.3 kg (25-50p, -0.43 SDS), the right upper arm was 13 cm, the right forearm 13 cm, the upper left arm 10.5 cm, and the right forearm was 10 cm. The distance between the fingers was 92 cm. Other system examinations were normal. Complete blood count, biochemical parameters, and thyroid function tests were normal. Madelung deformities were observed in the radiographs of the upper extremity. LWD was considered in patients with present findings. Karyotype analysis revealed 46,XX. *SHOX* (Xp22.3) gene deletion was detected in the patient who underwent advanced genetic examination.

We wanted to emphasize the importance of genetic studies in the etiology of short stature by presenting our case with LWD findings and *SHOX* gene deletion.

(P-37)

A Case of Marfan Syndrome Presenting with Transverse Striae of the Back

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Marfan syndrome is an autosomal dominant genetic disorder resulting from fibrillin gene mutation. The connective tissue in heart, eyes, skeletal, lungs, and central nervous system is affected.

A girl from non-consanguineous family was referred to pediatric endocrine department because of tall stature, joint pain for six months, and transverse striae of the back. It was learned from her family history that two uncles had tall stature and very long extremities. This 12-year-old girl was born with weight of 4000 g by caesarean section. On physical examination, height was 182.3 cm (>97p), height SDS 3.92, weight 67.1 kg (75-90p), weight SDS 1.75, body mass index 20.19, body mass index SDS 0.54, arm span 186 cm (>97p), and arm span SDS +4.5. On physical examination, the patient with the long-facial appearance had high-arched palate, long limbs and legs, purple-guinea-colored transverse striae of back, arachnodactyly, genu recurvatum, joint laxity, hypermobility, pes planus, scoliosis, and pectus excavatum. The Beighton score 7/9 for hypermobility and Tanner 4 for puberty were detected.

Full blood count, biochemical analysis, thyroid function, and pubertal hormone tests were found to be normal in terms of tall stature. Serum levels of IGF-1 and IGFBP-3 ranged from 0 to +1 SDS. Echocardiography revealed mitral valve prolapse. The eye examination was normal in terms of lens subluxation.

In this report, Marfan syndrome with tall stature and transverse striae of the back was presented. Early diagnosis and appropriate treatment will prevent the development of complications.

(P-38)

Diagnostic Algoritm in Two Different Cases with Subclinical Endocrinologic Problems

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Incomplete form of Di George syndrome (DGS) which is characterized by hypoparathyroidism, thymic aplasia, facial dysmorphism, and cardiovascular anomalies may present with subclinical endocrine problems and may result in delay in diagnosis.

Case 1: A 2-year-old girl born to unrelated healthy parents was consulted due to mild hypocalcemia before angiographic evaluation for tetralogy of Fallot. Anthropometric evaluation was appropriate for her age. She had perioral cyanosis, mild hypertelorism, high palate, and minor anomaly in her toe. She had borderline hypocalcemia, low parathormone, and high TSH levels in biochemical and hormonal evaluation. Thymus was absent in her chest X-ray. CD3, CD4, CD8, CD19 were low, total complement level, quantitative immunoglobulin levels, and in vitro lymphocyte transformation tests were normal. **Case 2:** A 31-day-old female patient born to unrelated healthy parents was consulted due to high TSH levels. Anthropometric evaluation was appropriate for her age. She had clubfoot, low-set ears, micrognathia, and high palate. In laboratory evaluation, hypocalcemia and high TSH level were determined. Ostium secundum ASD and bilateral hydronephrosis were observed in echocardiography and renal ultrasonography. Thymus gland was present in chest X-ray.

DOUBLE FISH analysis was performed. Case 1: Heterozygote 22q11 mutation was determined and the patient was diagnosed as having incomplete DGS. Case 2: Homozygote 22q11 deletion was determined and the patient was diagnosed as having DGS.

It's important to perform DOUBLE FISH analysis in cases with subclinical endocrine problems if incomplete DGS is suspected. Thus, major problems (such as graft versus host disease due to transfusion), which may patient face in the future, might be prevented.

(P-39)

A Novel *De Novo* Missense Mutation in HNF4A Resulting in Sulfonylurea-Responsive MODY

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Maturity-onset diabetes of the young (MODY) is a monogenic form of diabetes with autosomal dominant inheritance and usually develops before 25 years. Heterozygous inactivating hepatocyte nuclear factor 4A (HNF4A) mutation is a rare subtype of MODY.

A 14-year-old girl was admitted to our clinic due to fatigue and polyuria, and hyperglycemia was detected afterward. She was born full term with birth weight of 5500 g (4.9 SD score) and had no postnatal hypoglycemia. Her parents were not relatives and family history revealed no diabetes. Physical examination revealed a height of 163 cm (SD score 0.29), weight 64.7 kg (SD score 1.2), and body mass index of 24 kg/m^2 (SD score 1.2). Neither acanthosis nigricans nor striae were found. Laboratory analyses showed C-peptide 1.66 ng/mL (normal, 0.9-7.1 ng/mL), glycated hemoglobin (HbA1c) 8.8%, normal lipid profile, and negative autoantibodies regarding diabetes. Urine analysis showed 2+ glycosuria and no ketosis. We started only insulin glargine (0.2 unit/kg/day) with most probable diagnosis of MODY. Normal glycemia was improved and no hypoglycemia was seen with this treatment. HbA1c was decreased to 6.3%.

Genetic analysis revealed a *de novo* p.C93Y (c.278G>A) heterozygous novel change in the HNF4A. Insulin treatment was stopped and low-dose sulfonylurea (5.0 mg/day) initiated when the diagnosis of MODY 1 was proved. After five months of the treatment onset, fasting glucose was 111 mg/dL, insulin 11 IU/mL, C-peptide 2.2 ng/mL, and HbA1c was 5.8%.

Genetic testing should be considered to establish an accurate diagnosis and provide an opinion to determine the appropriate type of treatment.

(P-40)

Two Cases of Testicular Adrenal Rest Tumor (TART)

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Testicular adrenal rest tumor (TART) is a benign tumor which is seen in male patients who have congenital adrenal hyperplasia (CAH).

Case 1: A 24-year-old male was diagnosed with CAH. He took hydrocortisone treatment upto 18 years of age however discontinued it thereafter. Testicular mass was detected and right radical orchiectomy was performed; testicular tumor of adrenogenital syndrome was determined. On physical examination, height was 152 cm, weight was 47 kg, BMI was 20.3 kg/m^2. He had short fingers. In laboratory examination, 17-OHP 122 ng/mL (0.6-3.3), adrenocorticotropic hormone 118 pg/mL (< 46), free testosterone 34.4 pg/mL (57-178), DHEAS 378.4 µg/dL (85-690), and cortisol 5.2 µg/dL were detected. In CAH mutation screening, mutations in an allele (heterozygous) I2 splice and in the other allele (heterozygous) L307 frameshift were detected. Dexamethasone 0.75 mg once daily was initiated.

Case 2: A 38-year-old male has followed with diagnosis of Addison disease for 35 years. Right testicular tumor was defined as Leyding cell tumor in 2010. In scrotal USG, small multifocal lesions were detected and testicular biopsy was done which revealed testicular tumor of adrenogenital syndrome. He took 30 mg hydrocortisone once daily. On physical examination, height was 174 cm, weight 104 kg, and BMI was 34.4 kg/m^2. In laboratory examination, 17-OHP 157 ng/mL (0.6-3.3), adrenocorticotropic hormone 194 pg/mL (< 46), free testosterone 31.6 pg/mL (57-178), DHEAS 123.5 µg/dL (85-690), and cortisol 2.14 µg/dL were detected.

TARTs are usually seen bilaterally (83%) and histopathologically it is difficult to differentiate them from Leydig cell tumor. It should be kept in mind that testicular USG is of significant importance in early diagnosis of TART.

(P-41)

Hepatic Glycogenosis in a Patient with Type 1 Diabetes: Mauriac Syndrome vs. Congenital Glycogen Storage Disease

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We aimed to emphasize that the etiology of elevated liver enzymes should clearly be explained in type 1 diabetes mellitus patients.

A 20-year-old male who was on intensive insulin regimen with a history of type 1 diabetes for 11 years was admitted to our hospital with complaints of diarrhea and vomiting for three days. No other chronic diseases or complications of diabetes were present. Physical examination revealed temperature of 37.6 °C, pulse 138/min, blood pressure 86/40 mmHg, body weight 45 kg, and height of 155 cm, as well as Cushingoid face features and hepatomegaly. Examination of the other systems was unremarkable.

Laboratory findings were as followings: Venous plasma glucose 348 mg/dL, urine ketone 2+, and metabolic acidosis. The patient was managed by diabetic ketoacidosis protocol. The patient had also elevated ALT (167 U/L), AST (184 U/L), GGT (180 U/L), and ALP (140 U/L) levels. Abdominal ultrasonography performed to figure out the elevated liver enzymes showed grade 1 hepatosteatosis and hepatomegaly. Due to history of poorly controlled diabetes, hepatic glycogen deposition was also considered. Liver biopsy demonstrated PAS(+) granules in hepatocytes. We diagnosed the patient as Mauriac syndrome with the findings of growth retardation, poorly controlled diabetes, hepatomegaly, and hepatic glycogenosis. Genetic analysis was performed to exclude congenital glycogen storage disease type-1 (GSD-1). Heterozygous mutation was found in glucose-6-phosphatase (17q21,p.R83C), describing our patient as carrier. Although it is known that the carriers are asymptomatic, we assume that this mutation could contribute to hepatic glycogenosis. Diet and medical therapy were planned.

Hepatomegaly and elevated transaminases in type 1 diabetes patients may be caused by hepatic glycogenosis. In differential diagnosis of Mauriac syndrome, congenital glycogenoses should also be considered.

(P-42)

A Novel Mutation in *INSR* Gene in a Child Presenting with Acanthosis Nigricans

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Rabson-Mendenhall syndrome (RMS) is an autosomal recessive disorder resulting in severe insulin resistance due to defects in signaling through the insulin receptor. Symptoms of RMS include diabetes mellitus due to severe insulin resistance, acanthosis nigricans, impaired adipose tissue, and growth restriction. Herein, we report a case with RMS presenting with acanthosis nigricans due to a novel mutation in the *INRS* gene.

According to the past medical history, the patient was born with a birth weight of 3500 g. She was the first child of consanguineous parents. On physical examination, her weight was 18.7 kg (-0.08 SDS) and height was 98.7 cm (-2.6 SDS). Initial clinical findings showed severe acanthosis nigricans of the neck, axillae, the external genitalia and antecubital regions, generalized lanugo, abnormalities of the teeth, and dysmorphic face.

Initial laboratory tests showed normal fasting glucose (78 mg/dL), normal postprandial glucose (102 mg/dL), and extremely elevated fasting insulin (129 µIU/mL). After an overnight fast, an oral glucose tolerance test was performed and impaired glucose tolerance was detected. Sequence analysis of the *INSR* gene in the patient revealed a homozygous missense mutation in exon 11 at the nucleotide position c.861 (c861 C > A) resulting in a premature stop codon instead of tyrosine at codon 287 (p.Y287). Screening of relevant mutation was performed in the remaining family members. The father, mother, and a sibling were heterozygous.

We thought that our patent may have RMS due to her mild clinic signs and a novel mutation in *INSR* gene detected in molecular analyses.

(P-43)

Thyroid Hormone Resistance P453A Mutation

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Thyroid hormone resistance is a disease characterized by reduced sensitivity to thyroid hormone in cell membrane, altered metabolism and nuclear receptor. The clinic signs of thyroid hormone resistance are goiter, sinus tachycardia, attention deficit hyperactivity disorder; the laboratory signs are high level of free T4 and normal level of TSH.

A 10-year-old girl was admitted to our clinic with complaints of palpitation and nervousness. Her weight and height were 27 kg (3-10p) and 132.8 cm (3-10p), respectively. On physical examination, heart rate was 84 beats/min, blood pressure was 90/60 mmHg, and her thyroid was stage 1. Her thyroid function tests were as follows: total T_3 2.4 ng/mL (0.9-2.3), free T_3 6.17 pg/mL (1.7-3.7), total T_4 12.9 µg/dL (5.9-12.9), free T_4 2.33 ng/dL (0.7-1.48), TSH 3.29 µIU/mL, thyroglobulin 15.2 ng/mL (0.2-70), and negative antibodies of thyroglobulin and thyroperoxidase. In the genetic analysis of the patient suspected of having thyroid hormone resistance, the P453A c.1357C > G mutation was detected to be heterozygous on the exon 10 of the *THRB* gene. Beta-blocker therapy was initiated in the patient who was still complaining of palpitations and tachycardia.

Among *THRB* gene mutations, 453 mutation is the most common one. In our case, the receptor affinity of T_3 was reduced to 17% as a result of alanine substitution of proline amino acid due to guanine transversion instead of cytosine in codon 453 at exon 10. This mutation has been reported in six patients in the literature and it is noteworthy that four of the patients are of Turkish origin.

(P-45)

A Case of Vanishing Testis Syndrome

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Gender differentiation results from the interaction of hormonal and genetic factors. According to the sex chromosomes of the individual and the effect of transcriptional factors, testis or ovary develop from the embryonic bipotential gonads.

A boy from non-consanguineous family was admitted to pediatric endocrine department because of non-palpable testes in the scrotum. A 7-year and 2-month-old boy was born with weight of 2500 g by vaginal delivery. It was learned from his previous history that he had undergone laparoscopy and no testes had been found in the abdomen. On general examination, height was 133.6 cm (97p), height SDS 2, weight 27 (75-90p), and weight SDS was 0.89. The patient was conscious, oriented, and well-nourished with normal secondary sexual characteristics for his age. On local genital examination, he had 5 cm stretched penile length, 1 cm penile width, no axillary and pubic hair. Right and left scrotal sac appeared empty.

For finding location of testes, ultrasonography and MRI were done and no testes was found in abdomen, inguinal canal, or scrotum. Karyotyping revealed a normal 46,XY karyotype. Serum follicle-

stimulating hormone, luteinizing hormone, and total testosterone levels were 33.02 mIU/mL (normal reference range <6.7), 0.54 mIU/mL (normal reference range 0.3-6.0), and 5.19 ng/dL (normal reference range <7), respectively. Serum testosterone levels were not increased in response to 1500 units/dose HCG stimulation test for 3 days. The diagnosis of vanishing testis was confirmed and hormone replacement therapy was planned to start during puberty.

Early diagnosis and appropriate treatment will prevent the development of hypogonadism complications.

(P-46)

Warburg Micro Syndrome: A New Case from Consanguineous Parents

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Warburg micro syndrome (WARBM) is a rare autosomal recessive disorder characterized by postnatal severe intellectual disability, microcephaly, ocular findings such as congenital cataract, microcornea, microphthalmia and optic atrophy, and hypogonadism. *RAB3GAP1* mutations are mostly causative. This child was presented because of having two patients from the same family. First son of the family had WARBM and he died.

A 12-month-old boy was admitted to our clinic because of congenital cataracts, micropenis, and cryptorchidism. Parents were second cousins. Birth weight was 2800 g. At 2 months of age, he underwent bilaterally phacoemulsification. His weight was 6.8 kg (<3p), length 75.5 cm (25-50p), and head circumference was 41 cm (<3p). He had low-set and large ears, a prominent nasal root, ptosis, high-arched palate, and micrognathia. Ophthalmological examination revealed hypotelorism, microphthalmia, and microcornea. He had truncal hypotonia, increased muscle tone in both legs, poor head control, and was unable to sit without support. He had bilateral cryptorchidism, a micropenis (stretched penile length of 20 mm), and scrotal hypoplasia. USG revealed both testicles within the inguinal canals. Karyotype was 46, XY, inv(9)(p12q13). Failed to get visual message as a result of Flash VEP. Cranial MRI showed atrophy of the corpus callosum and cerebral cortex. Sequence analyses of the *RAB3GAP1* gene revealed that he was homozygous for the splice donor mutation c.748+1G>A. His deceased brother possessed the same mutation. Both parents were heterozygous for the mutation.

WARBM is rarely presented in siblings. The importance of pre-conception genetic counseling in the family who has children with same disorders is highlighted.

(P-47)

Williams Syndrome Associated with Isolated Growth Hormone Deficiency: Is It Just a Coincidence?

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Williams-Beuren syndrome (WBS) is a rare disorder caused by chromosome 7q11.23 deletion. Clinical manifestations are a happy looking dysmorphism, moderate mental retardation, growth retardation, and congenital heart defects (CHD). Short stature is found in about 50% of children with WBS, however, it is generally not severe. Here, we report a case of WBS associated with growth hormone deficiency (GHD).

The patient was the first child of healthy, non-consanguineous parents. He was born at term with weight of 2500 g (3p), length 48 cm (3p), and head circumference (HC) of 33 cm (3p). At age 3 years, he was referred for the first time because of dysmorphism and CHD. Serum calcium levels were elevated. He had severe growth retardation. His height was 73.6 cm (≤3p), weight 7300 g (≤3p), and HC was 43.5 cm (below -2 SDS). The karyotype was normal. FISH analysis showed hemizygously deleted 7q11.23. Measures yielded during endocrine evaluation were indicative of severe GHD. Treatment with hGH 1 U/day was started to which our patient responded well.

Short stature is found in about 50% of children with WBS. It is usually not severe and the postnatal overall growth is frequently along the 3p. For some WBS patients on the contrary, growth retardation is severe. To the best of our knowledge, there are only 3 patients with WBS reported to have associated GHD. The pathogenesis of GHD is unclear. A hypothalamic rather than pituitary defect is suggested. We recommend evaluation of growth hormone or at least screening by IGF-I measurements in all patients with microdeletions and unexplained short stature.

(P-48)

Atypical LMNA Mutation in EXON 11 Associated with a Milder Clinical Outcome in Dunnigan-Type Familial Partial Lipodystrophy

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Dunnigan-type familial partial lipodystrophy (FPLD2) is a rare genetic disease associated with loss of subcutaneous adipose tissue and accompanying metabolic involvement such as diabetes, hyperlipidemia, and hepatosteatosis. We aimed to present a rare family with FPLD2 caused by an atypical Lamin A/C gene (LMNA) mutation.

The proband of this family was a 43-year-old female patient who was diagnosed with FPLD2 caused by a heterozygous missense mutation, R582H (c.1745G→A) in exon 11. Here, we report her prospective 8-year follow-up as regard to metabolic complications and end-organ abnormalities.

Due to adipose tissue dysfunction, she developed type 2 diabetes, hypertriglyceridemia, and hepatosteatosis at her thirties. In contrast to many patients with typical FPLD2, her diabetes was well regulated by metformin monotherapy. Lifestyle management, dietary modifications, and fenofibrate monotherapy successfully treated the hypertriglyceridemia. No complication of diabetes has developed. Cardiac and neurological regular assessments were normal. Her father was also diagnosed with FPLD2 caused by the same point mutation. Similarly, his diabetes and hypertriglyceridemia could be easily managed by lifestyle modifications, metformin, and fenofibrate and no end-organ complication was observed.

LMNA undergoes alternative splicing to produce two nuclear laminar proteins - lamin A and C. Multiple missense mutations associated with FPLD2, most of which are located in exon 8 at the codon position 482, have been reported. The missense mutation in our patient was also associated with FPLD2, however, the clinical reflection was somehow milder. This could be explained by the fact that exon 11 mutation affects only lamin A, unlike exon 8 mutation which affects both lamin A and C proteins.

(P-49)

A Novel Mutation in *AMHR2* Gene in Two Siblings with Persistent Müllerian Duct Syndrome

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Persistent Müllerian duct syndrome (PMDS) is a rare form of male 46,XY disorder of sex development characterized by failure of Müllerian duct to regress in a male fetus during embryonic development. Approximately 45% of cases with PMDS are due to AMH deficiency (type 1), while 40% of cases are due to receptor defects (type 2). We report a novel mutation in *AMHR2* gene in two siblings who presented with bilateral undescended testis.

A 4-year-old boy presented with bilateral undescended testis. At physical examination, the right testis was palpated in the inguinal canal, while the left testis could not be palpated. External genitalia were phenotypically normal male. Ultrasonography revealed absence of left testis and atrophy of right testis. Testosterone response to β-HCG stimulation test was positive. Laparoscopy demonstrated the right testis in the inguinal canal, the left testis behind the urinary bladder, in addition to uterus behind the urinary bladder. His 2-year-old brother also presented with right undescended testis. At physical examination, the right testis could not be palpated and the left testis was palpated in the inguinal canal. External genitalia was phenotypically normal. During surgery, rudimentary uterus was identified between intraabdominal testes. Presence of Müllerian duct structures in cases with karyotype 46,XY confirmed the diagnosis of PMDS. There was second cousin marriage between parents of cases. Homozygous p.V458L(c.1372G>T) mutation in *AMHR2* gene was found.

We report a novel mutation in *AMHR2* gene as a cause of PMDS. PMDS is a rare condition; however, it must be considered in the differential diagnosis of cryptorchidism with normal male genitalia.

(P-50)

A Case of *SHOX* Gene Deletion Diagnosed By Microarray

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SHOX (Short Stature Homeobox) which is located at Xp22.33 is evolutionary well-conserved developmental gene expressed in osteogenic cells. *SHOX* is one of the suspected components of the short stature in Turner syndrome cases. Also functional homolog of *SHOX* gene is located at Y chromosome. Haploinsufficiency of genes on the X chromosome results in Turner syndrome.

Here, we present a 26-month-old female referred to genetic counseling because of short stature and developmental delay. Her height was 71 cm (< 3 percentile), weight 9.5 kg (< 3 percentile). She had frontal bossing, hypertelorism, and bilateral mesomelic short upper extremities. Her motor and mental developments were normal. Bone X-ray survey revealed a thickness of long bones and delayed bone age.

Karyotype showed an extra genomic material at the p arm of the X chromosome. We performed chromosomal microarray. Approximately 18 Mb gain at the short arm of chromosome 6 and 680 Kb deletion at the p arm of X chromosome were detected.

Three genes including *SHOX* were deleted from the involved region of X chromosome. A gain of 63 genes located at chromosome 6p was observed, which resulted in partial trisomy of 6p. Effects of partial trisomy 6p in our case is not clear, but the deleted *SHOX* is suspected to be the reason for short stature and delayed bone age.

(P-51)

HOXC4 Gene is Possibly Responsible for Lin-Gettig Syndrome

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Lin-Gettig syndrome, described by Lin and Gettig in 1990, is a very rare autosomal recessive disease. The syndrome is characterized by craniosynostosis, severe mental retardation, absence of corpus callosum, dysmorphic facial features, camptodactyly, and hypogonadism. The molecular etiology of the syndrome has not yet been identified. In this report, we present a patient diagnosed as having Lin-Gettig syndrome via clinical findings. Molecular genetic studies have revealed that *HOXC4* may be the responsible gene for this syndrome.

Due to motor-mental retardation and abnormal facial features, a 15-month-old boy was referred to our department for genetic counselling and differential diagnosis. On physical examination, his weight, height, and head circumference were measured to be 9.4 kg (10^{th}-25^{th} centile), 74 cm (3^{th}-10^{th} centile), and 43 cm (< 3^{th} centile), respectively. He had microcephaly and trigonocephaly, proptosis, downslanting palpebral fissures, midface hypoplasia, depressed nasal bridge, short columella, micrognathia, and low-set dysplastic ears. His genital examination showed micropenis, bifid scrotum, and cryptorchidism. Craniosynostosis was diagnosed using 3D computed tomography. Brain magnetic resonance imaging revealed a Chiari I malformation.

Exome sequencing of the proband showed a homozygous c. 410C > G (p.P137R) mutation in *HOXC4* gene. The parents carried this mutation heterozygously. It has been considered that mutations in *HOXC4* gene are the most probable candidate responsible for the underlying molecular etiology in the syndrome.

This is the first study in the literature defining a gene considered to be responsible for Lin-Gettig syndrome.

(P-52)

POU1F1 and *PROP1* Gene Mutations in 4 Cases of Combined Pituitary Hormone Deficiency

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Combined pituitary hormone deficiency (CPHD) is characterized by the impaired production of GH together with one or more of other pituitary hormones. The most commonly recognized genetic defects associated with CPHD include mutations within *PROP1*, *POU1F1*, *HESX1*, *LHX3*, *LHX4*, *OTX2*, *GLI2*, and *SOX3*.

The phenotype connected to *POU1F1* mutations is characterized by profound GH and PRL deficiencies, variable degrees of TSH deficiency, severe proportional short stature, atypical facies, and feeding difficulties in infancy. Patients harboring mutations within *PROP1* gene present with GH, PRL, and TSH deficiencies in addition to variable defects in luteinizing hormone/follicle-stimulating hormone and adrenocorticotropic hormone secretion. *PROP1* mutations are the most common known genetic cause of CPHD cases.

Here, we present 3 cases with *POU1F1* mutation and 1 case with *PROP1* mutation, who were molecularly diagnosed in Medical Genetics Department of Ege University.

The three cases (1 female, 2 males) carrying *POU1F1* mutations all had short stature. One male case with a novel mutation, p.K216T, also presented with micropenis in addition to short stature. The other mutations detected in *POU1F1* gene were S50A, R265W; S50A being novel. The case with *PROP1* mutation also had short stature and micropenis. Molecular analysis revealed a frameshift p.L102CfsX8 mutation in the *PROP1* gene. Biochemical testing showed PRL and GH deficiencies in all cases. Two cases with *POU1F1* defect and the case with *PROP1* defect also had central hypothyroidism.

It is considered that in patients with growth retardation together with combined pituitary hormone deficiency, *POU1F1* and *PROP1* gene mutations should be investigated. In this study, two novel *POU1F1* mutations were detected for the first time.

(P-53)

FGFR2 Gene Mutations in Patients with Syndromic or Isolated Craniosynostosis

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Craniosynostosis, premature closure of one or more cranial sutures, may occur in both non-syndromic and syndromic forms. Birth prevalence of craniosynostosis is 1/ 2,100–1/2,500. *FGFR2*, *FGFR3*, *FGFR1*, *TWIST1*, and *EFNB1* genes play a role in the syndromic craniosynostosis presenting with craniofacial abnormalities, including hypertelorism, proptosis, and midfacial hypoplasia. Limb, cardiac, central nervous system, and tracheal malformations have also been described. Mutations in the *FGFR2* gene located on 10q26 that encode fibroblast growth factor receptor 2 is responsible for a part of the syndromic craniosynostosis. The aim of this study was to determine *FGFR2* gene mutations in 85 craniosynostosis cases including Apert, Pfeiffer, and Crouzon syndromes, and isolated craniosynostosis patients who were referred to molecular genetics laboratory of Medical Genetics Department, Ege University between 2010 and 2016.

Sequence analysis was performed on 2 exons (exons 7-8) of the *FGFR2* gene in 85 cases referred for pre-diagnosis of craniosynostosis between 2010 and 2016. Sanger sequencing analysis method was used for sequence analysis.

Mutations were detected in twenty of the cases (23%). The frequency of *FGFR2* mutation in this study was 20% S252W and P253R (4 cases), 15% Y382C (3 cases), 10% Y308C (2 cases) and 5% A314S, A266P, P253A, W290C, W290R, S351C, S252P (1 case).

In syndromic and isolated craniosynostosis patients, the analysis of exons 7 and 8, which is one of the mutational hot spot of *FGFR2* gene, allows diagnosis in 23% of patients. It has been concluded that performing complete *FGFR2* gene analysis will provide larger numbers of molecular diagnosis.

(P-54)

The Mutation Spectrum of *DHCR7* Gene and Two Novel Mutations

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Smith-Lemli-Opitz syndrome (SLOS) is a rare autosomal recessive syndrome. It is one of the 46,XY disorders of sexual development. Molecular defects in *DHCR7* gene are responsible for this syndrome. In this study, the mutation spectrum of *DHCR7* gene in SLOS patients has been evaluated.

Thirteen patients from 11 families carrying mutations in the *DHCR7* gene were included in this study. Seven different *DHCR7*

gene mutations (4 missense: p.T93M, p.R352W, p.Y432C, p.E448K; 2 nonsense: p.W151X, p.Q259X; and one splice site: c.831 + 1G > C) were detected. p.T93M was the most frequent (57% of all alleles) mutation. Two of the seven mutations (p.Q259X, c.831 + 1G > C) were defined for the first time in this study.

This study defines the mutation spectrum and genotype phenotype correlation of *DHCR7* gene within the Turkish SLOS patients. As seen in other Mediterranean populations, p.T93M mutation was the most frequent mutation observed in our patients.

(P-55)

Anthropometric Measurements and Complications of Achondroplasia Patients

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Achondroplasia is the most common reason of inherited disproportionate short statue. It is caused by mutations in the *FGFR3* (fibroblast growth factor receptor-3) gene. In this study, we aimed to evaluate the anthropometric measurements and complications in achondroplasia patients.

In this study, using Sanger sequencing or next-generation sequence analysis, *FGFR3* gene mutations were detected in 29 patients (achondroplasia/hypochondroplasia: 15/14) between 2012 and 2016. Nine of the 15 achondroplasia patients and one of the 14 hypochondroplasia patients had been followed by both Pediatric Genetics and Pediatric Endocrinology Subdivisions of Ege University Medical Faculty. Fifty percent of patients were female and 50% were male. Median age was 27 months (min 9-max 96 months). Anthropometric measurements of the patients were found to be in normal ranges using growth curves specific for achondroplasia patients reported by Horton et al. When evaluated according to normal growth curves, mean standard deviations of height, weight, and head circumference were -4.45 (± 1.59), -1.38 (± 1.15), and 1.99 (± 1.20), respectively. In one patient, foramen magnum stenosis and cervicospinal junction compression were observed. Another patient had mental retardation and epilepsy.

It has been considered that growth of achondroplasia patients can be maintained in the limits of achondroplasia patients when appropriate follow-up is performed. They should be carefully evaluated for neurological and orthopedic complications.

(P-56)

Mutation Spectrum of *GCK*, *HNF1A*, and *HNF1B* in MODY Patients and 40 Novel Mutations

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MODY (maturity onset diabetes of the young) is a monogenic diabetes mellitus caused by pancreatic beta cell dysfunction. It has been classified into 9 groups according to the underlying molecular etiology. Mutations in the genes encoding the nuclear transcription factor 1 homeobox A *(HNF1A)* and the enzyme glucokinase *(GCK)* are the most common causes of MODY. Additionally, *HNF1B* gene is responsible for 5% of the disease. The aim of this study was to investigate the mutation spectrum of *GCK*, *HNF1A*, and *HNF1B* genes in MODY patients.

Molecular test results of 152 patients carrying mutations in *GCK*, *HNF1A*, or *HNF1B* genes were evaluated. Rate of mutations detected in GCKL, *HNF1A*, and *HNF1B* genes were 84%, 13%, and 3%, respectively. Fifty-seven different mutations (40 missense, 8 nonsense, 7 frameshift, 1 in-frame deletion, and one splice site) in *GCK*, 15 different mutations (11 missense, 3 frameshift, and one 3' UTR) in *HNF1A* and 4 different mutations (2 missense, one frameshift, and one indel) in *HNF1B* were found. Thirty-tree, 5, and 2 mutations were detected as novel mutations in *GCK*, *HNF1A*, and *HNF1B* genes, respectively.

Definition of molecular etiology in MODY patients is important for giving appropriate genetic counseling and disease management. The most commonly affected gene has been found to be *GCK* gene among the MODY patients studied. In the genes *GCK*, *HNF1A*, and *HNF1B*, 40 mutations have been defined for the first time in this study.

(P-57)

MEN 2A Family

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MEN 2 is a rare genetic disorder with autosomal dominant inheritance. Here, we present a family in which MEN2A was detected in the index case and two brothers had detected pheochromocytoma and medullary thyroid cancer.

MEN 2A index case;

Index case: A thirty-six-year-old male patient presented with headache, sweating, and palpitations. Urine catecholamines

were significantly higher. A bilateral adrenal mass was detected and bilateral surrenalectomy was performed. Plasma calcitonin level was high. A hypoechoic, coarse calcific thyroid nodule was detected. The patient underwent total thyroidectomy and neck dissection. The parathormone (PTH) level was normal. The RET mutation was positive in the patient. It was decided to screen the family. Second case: A 50-year-old male patient was called for MEN 2A family screening. Bilateral adrenal mass was detected. Bilateral surrenalectomy was performed. Calcitonin level of 267 pg/mL was detected. Hypoactive thyroid nodule aspiration was reported as AUS. Total thyroidectomy and central neck dissection were applied to the patient. Cranial involvement was also observed in the PET/CT scan for metastasis. A mass in the left cerebellum (hemangioblastoma?) was detected in brain MR. Third case: A forty-six-year-old female patient was evaluated; a mass with size of 56x64x50 mm in the left adrenal and normal right adrenal were detected. Metanephrine and normetanephrine were significantly high in the urine. Calcitonin level was significantly high. Firm thyroid nodule was detected. PTH was normal. Left adrenalectomy and total thyroidectomy were planned. The patient refused to be treated.

MEN 2A syndrome is the most common medullary thyroid cancer. Bilateral pheochromocytoma is common. Hyperparathyroidism is observed in 20-30 % of patients.

(P-58)

Investigation of Androgen Receptor Gen Mutation Spectrum in the Turkish Patients with Disorder of Sex Development

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Androgen insensitivity syndrome (AIS) is an X-linked recessive condition resulting in a failure of normal masculinization of the external genitalia in chromosomally 46,XY individuals. This failure of virilization can be either complete androgen insensitivity syndrome (CAIS) or partial androgen insensitivity syndrome (PAIS), depending on the amount of residual receptor function. Mutations in the AR gene on chromosome Xq12 cause AIS. In this study, we aimed to investigate the mutation spectrum in Turkish patients who had AR mutation analysis with suspected gender development disorder and AR insensitivity syndrome.

The *AR* gene from the DNA material isolated from the peripheral blood of patients was amplified using appropriate primers and sequenced using the new-generation sequence analysis technique on the Mi-Seq device.

In this study, molecular analysis results of 383 individuals who underwent AR genetic analysis in Ege University Medical Genetics Department between 2011 and 2016 were evaluated retrospectively. There were 44 mutations in these cases. Of the 44 cases detected in the mutation, 16 were affected and the karyotype was 46,XY. 28 of them are the 46,XX carrier mothers, carrier relatives, or siblings of the affected cases.

New mutations were detected in our studies between 2011 and 2016-L57Q, T576I, D691Y, P672R, Q739E, p.R544KfsX8, c.1745_1747delTCT, F726S, L881V, R102G, and L863F. Different mutations can be detected in AR gene in Turkish society. In cases with disorder of sex development, *AR* should be examined.

(P-59)

A Novel *HESX1* Mutation in a Case with Panhypopituitarism

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Pituitary gland insufficiency (hypopituitarism) is a clinical condition that results in inadequate production and release of pituitary hormones. The deficiency of one or more pituitary hormones is named partial hypopituitarism and the deficiency of all pituitary hormones is named panhypopituitarism. Hypopituitarism can be attributed to inherited or acquired causes. Our aim was to determine the molecular diagnosis in our panhypopituitarism patient with *HESX1* gene sequence analysis.

A 21-year-old woman was referred to our clinic with primary amenorrhea. Her medical history included use of growth hormone, thyroid hormone, and estrogen. Cranial MRI findings were consistent with empty sella syndrome. In the family history of the case, there was no consanguinity between the parents and no similar patient in the family. Based on findings and laboratory results, the diagnosis of panhypopituitarism was considered; *HESX1* gene sequence analysis from patient's peripheral blood revealed a heterozygous p.R128K mutation.

HESX1, *POU1F1*, *PROP1*, *LHX4*, *LHX3*, and *OTX2* genes have been associated with combined pituitary hormone deficiencies to date. The R128K mutation in the *HESX1* gene has not been previously reported, and *in silico* predictions for that mutation suggested that this might be the disease-causing variant. This case report provides a contribution to the literature by defining a new mutation in *HESX1* gene.

(P-60)

Homozygous *SHOX* Gene Deletion Detected by Array-CGH in a Girl with Langer Mesomelic Dysplasia

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Langer mesomelic dysplasia (LMD; MIM 249700) is characterized by hypomelia with severe hypoplasia of ulnae and fibulae, and bowed, thickened radii and tibiae, causing deformities of the hands and feet. LMD is caused by homozygous mutations in the *SHOX*/*SHOXY* (short stature homoebox) gene, of which bi-allelic mutations or gross deletions cause Leri-Weill dyschondrosteosis (LWD). The aim of our study was to determine the genetic etiology of LMD.

Our patient was a 16-year-old female with LMD, the second child of healthy first-cousin parents. She had micrognathia, disproportionate short stature with various musculoskeletal findings (absence of the distal flexion creases of the 3rd, 4th, and 5th fingers on the right hand and camptodactyly of the 3rd, 4th, and 5th fingers on the left ; tibial bowing). X-rays revealed hypoplasia of ulnae, fibulae, and the mandible.

Chromosome analysis and FISH investigation by using *SHOX* gene probe revealed normal results. The intended sequence analysis with the aim of investigating possible mutations failed due to obtaining PCR amplification with no product. Array comparative genomic hybridization (a-CGH) study showed a 174 kb homozygous deletion, encompassing the *SHOX* gene. Proband's parents were heterozygous for the same deletion by a-CGH.

The addition of the a-CGH study to the algorithm is also important in terms of diagnostic contribution in the search for mutations in the *SHOX*/*SHOXY* gene responsible for the formation of the LMD phenotype.

(P-61)

Four 46,XY DSD Cases with Novel Mutations in AR and *SRD5A2* Genes

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Androgen receptor (AR) defects and 5α-reductase (5α-RD) deficiency in 46,XY disorders of sexual development (DSD) present with indistinguishable phenotype. Affected individuals can present with a wide spectrum, from a female genital tract to ambiguous genitalia and mild virilization. The hemizygous mutations in the AR (Xq11.2-q12) encoding AR are associated with X-linked androgen insensitivity, and bi-allelic mutations in *SRD5A2* cause enzyme deficiency, converting testosterone (T) to dihydrotestosterone (DHT). Based on genetic diagnostic algorithm, *SRD5A2* is screened when T/DHT is >10, and AR is screened when < 10, and vice versa for cases with unidentified mutations, presenting with locus and allelic heterogeneity. Identifications of mutations responsible for phenotypes is effective in genetic counseling, managements, and follow-ups.

In this study, we aimed to investigate the genotype-phenotype relationship by evaluating clinical, hormonal, and genetic findings of four cases with ADS or 5α-RD deficiency in 46,XY DSD.

Clinical manifestations and hormone levels (basal luteinizing hormone, follicle-stimulating hormone, T, DHT, T/DHT ratio with short-term stimulation of hCG test) were evaluated and chromosomal abnormalities were excluded in cases with 46,XY. AR (NM_000044.3) and *SRD5A2* (NM_000348.3) were evaluated by Sanger sequencing and variants were investigated by using molecular databases.

AR was screened in three cases whose T/DHT < 10 (Case 1-2-3) revealed three novel variants in each: synonym (c.330G > C; p.Leu110 =), frameshift (c.2585delAGCTCCTG; p.K862Rfs*16), and missense (c.2084C > T; p.Pro695Leu). *SRD5A2* was screened in one case whose ratio was >10 and revealed two different variants (one known and one novel) in compound heterozygous status, confirmed by parental testing; c.[164T > A];[269A > C] (p[Leu55Gln];[His90Pro]. The all novel mutations were analyzed by *in silico* programs and family segregation for inheritance model.

(P-62)

PTPN11, *SOS1*, and *BRAF* Gene Mutation Spectrum in RASopathies in Molecular Diagnosis

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RASopathy is a group of clinically defined medical genetic syndromes that are caused by germline mutations in genes encoding the Ras/mitogen-activated protein kinase (MAPK) pathway components or regulators. Noonan, LEOPARD, cardio-phasio-cutaneous, Costello, Legius syndrome, and neurofibromatosis type 1 are included in this group. The aim of this study was to evaluate the *PTPN11*, *SOS1*, and *BRAF* gene mutation spectrum of 70 patients with molecular diagnosis upon the prediagnosis of CFC and Noonan syndrome in RASopathy spectrum between 2008 and 2016 in Ege University Medical Faculty Medical Genetics Department.

Sequence analysis was performed on all coding exons and flanking intronic regions of the *PTPN11* gene, exons 6, 7, 8, 10, and 16 of *SOS1* gene, and exons 6, 11, 12, 14, and 15 of *BRAF* gene in 403 cases referred with prediagnosis of RASopathy between 2010 and 2016. Sanger sequencing analysis method was used for sequence analysis.

Mutations were detected in seventy of the cases (17%). In 63 cases, 28 different mutations were detected in the *PTPN11* gene. The frequency rates of *PTPN11* mutation in this study were as follows: p.N308D (26%), p.Y63C (6%), p.I282V (5%), p.M504V (5%), p.T468M (5%), and p.Y62D (5%). In 4 cases, 3 different mutations were detected in the *SOS1* gene. Mutations were identified as p.R522K, p.I600V, and p.E846K. In 3 cases, 3 different mutations were detected in the *BRAF* gene. Mutations were identified as p.E501K, p.N581D, and p.A481E.

In our study, we presented the largest RASopathy mutation spectrum in Turkey to date and we demonstrated that the mutation spectrum is also highly heterogeneous in these clinically heterogeneous group diseases.

FREE COMMUNICATIONS

(FC-01)

Impact of *CYP21A2* Gene Mutations on Clinical Management of Congenital Adrenal Hyperplasia

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Congenital adrenal hyperplasia (CAH) is a defect of cortisol biosynthesis. The most common cause of CAH is 21-hydroxylase deficiency (21-OHD) caused by *CYP21A2* gene mutations. 21-hydroxylase activity is correlated with different clinical presentations such as salt-wasting (SW), simple-virilizing (SV), and non-classical (NC) CAH. We aimed to determine the *CYP21A2* gene mutations and evaluate the genotype-phenotype correlation in 21-OHD patients to value the impact of these mutations for clinical management.

CYP21A2 gene mutation analysis with respect to common mutations P30L, IVS2, I172N, cluster E6, V281L,Q318X,R356W, Del 8-bp E3, P453S, R483P, L307 frameshift, large deletions, and conversions was performed by different methods namely RFLP, MLPA and reverse-hybridization, in 42 CAH patients from 38 families.

The mean age of the patients was 2.5 years. Ambiguous genitalia (45.2%) and vomiting/weight loss (23.8%) were the most common clinical presentations. 50% of the patients were in SW, 33.3% in SV, and 16.6% in NC forms. Mutations were found in 94% of 84 alleles. 88.1% of the patients had more than one mutations. 59.5% of the patients presented with homozygous genotype, whereas 28.6% were compound heterozygous. The most common mutations were IVS2 (22.6%), I172N (22.6%), Q318X (15.4%), and large deletions (14.2%). Q318X, large deletions, R356W, and cluster E6 mutations were more correlated to SW, I172N was more common in SV, and V281L was seen more frequently in NC.

Genotypes were well-correlated with phenotypes within clinical subtypes in most of the patients. The most common mutations were IVS2 and I172N in our study group. We believe that these data as well as others in the literature will serve for better genetic counseling in daily practice of CAH.

(FC-02)

Six 11-Beta Hydroxylase Deficiency Patients: Identification of Two Novel Mutations

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In this study, we aimed to define the molecular spectrum of *CYP11B1* gene mutations in 6 Turkish patients and to evaluate the phenotype-genotype correlation.

In patients who were considered to have 11-beta hydroxylase deficiency by Endocrinology Department and Pediatric Endocrinology Department, *CYP11B1* gene sequence analysis using a next-generation sequencing platform was performed in Medical Genetics Department, Faculty of Medicine, Ege University. Mutations detected were then confirmed by Sanger sequencing method.

In this study, 7 different *CYP11B1* gene mutations were detected in 6 patients who were referred to molecular analysis due to sex development disorder. Four patients carried the same mutation on both alleles, whereas 2 patients were compound heterozygous. Cardinal phenotypic features of the patients were ambiguous genitalia, hypertension, hypokalemia, and gynecomastia. Two of the 7 mutations were detected for the first time in this study. These were p.R120G and p.A199P mutations.

In cases presenting with adrenogenital syndrome, if their endocrine test results are consistent with 11-beta hydroxylase deficiency, molecular analysis should be performed.

(FC-03)

17-Hydroxylase Deficiency: Rare Cause of Delayed Puberty

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17-hydroxylase deficiency (17OHD) is a very rare disorder characterized by glucocorticoid deficiency, hypergonadotropic hypogonadism, hypertension, and hypopotassemia. Mutations in the *CYP17A1* gene cause 17OHD. Herein, we present three adolescents, one single and two cousins, with delayed puberty.

The patients were raised as girls. All of the patients were pre-pubertal. Initial clinical findings are given in the Table 1. Hydrocortisone, 17-beta estradiol, and antihypertensive treatments were initiated. First case achieved Tanner 5 breast development at 15.64 and had menarche at 15.72 years old. Alendronate was started due to osteoporosis (L-L4 BMD was -3.1). Second girl achieved Tanner 5 breast development at 15.08 and had menarche at 16.64 years old. The third patient could only been followed for six months because of advance age. A known mutation in the first patient and a novel mutation in the second patient were found in the *CYP17A1* gene.

Adrenal functions as well as gonadotropins should be examined in adolescent girls with no thelarche and pubarche associated with hypertension, and 17OHD should not be forgotten.

Table 1. Initial clinical findings

	Case 1	Case 2	Case 3
Karyotype	XX	XX	XY
Age, years	12.80	14.24	18.16
Height SD	-1.29	-2.10	-0.52
Weight SD	-0.96	-0.77	1.61
BP mm Hg	145/120	171/119	165/125
Follicle-stimulating hormone, mIU/mL	31.82	84.15	45.17
Luteinizing hormone, mIU/mL	11.86	26.46	35.54
Adrenocorticotropic hormone, pg/mL	140	107	99
Stim. Cortisol, ug/dL	3.46	0.76	< 1
Na, mEq/L	141	141	140
K, mEq/L	3	3.5	3.9
DOC, pmol/mL, (0.12-0.6)	11.9	2.76	2.58

Cases	Genomic	cDNA	Protein
1	g.6452G > A	c.1319G > A	p.R440H
2	g.276_280delCCCTG	c.104_108delCCCTG	p.P35Rfs*15

(FC-04)

Investigation of Association Between Paraoxonase-1 L55M (RS854560) and Q192R (RS662) Polymorphisms and Potential Atherosclerotic Risk Factors in PCOS Patients

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The aim of this study was to examine the frequency of potential atherosclerotic risk markers Q192R (rs662) and L55M (rs854560) in patients with PCOS and control group in Turkish women.

Blood samples were collected from 151 patients with PCOS and 52 healthy women at Recep Tayyip Erdoğan University Hospital, Rize. All individuals underwent an evaluation of clinical examination and transabdominal ultrasound. Genomic DNA was extracted from the samples. RFLP method was performed following the amplifications of the target regions. The L55M and Q192R polymorphisms were detected by AlwI and NlaIII digestion, respectively. The genotyping results of 88 samples of this cohort were also confirmed by DNA sequencing.

Patients with 192QR/192RR genotypes had a 2.5-time higher risk of representing PCOS compared to the individuals with 192QQ genotype. Differences in genotype and allele frequencies of PON1-55 were not found to be significant. Q192R (AUC: 0.613, $p = 0.017$) and BMI (0.618, $p = 0.012$) were established to be significant predictors of PCOS in a model including fasting glucose, insulin, HOMA-IR, total cholesterol, triglyceride, and LDL/HDL ratio as covariates (AUC: 0.655, $p = 0.001$). Q192R was more strongly correlated with PCOS than previously suggested atherosclerotic risk factors, BMI, metabolic syndrome (MetS), and insulin resistance (IR).

Q192R discriminates the patients with PCOS from controls significantly. Although further studies are needed, we suggest that individuals carrying an R allele are at a higher risk of developing PCOS in Turkish women. Q192R may be suggested to be a surrogate and robust predictive marker for the risk of developing PCOS and atherosclerosis in individuals.

(FC-05)

Hyperandrogenism and Skeletal Dysplasia: Evaluation of 7 Patients with *PAPSS2* Gene Mutation

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The synthesis of PAPS (3-phosphoadenosine 5-phosphosulfate) - a sulfate donor - is catalyzed by two isoenzymes (PAPS synthase1 and PAPS synthase 2). PAPSS1 is ubiquitously expressed in human tissues, including cartilage. *PAPSS2* shows a restricted expression pattern and is the major isoform involved in cartilage growth. *PAPSS2* is responsible from the sulfation of dehydroepiandrosterone (DHEA) which is an androgen precursor. Impaired sulfation of DHEA leads to increase in the levels of active androgens and clinical findings of hyperandrogenism occurs. Homozygous mutations in the *PAPSS2* gene lead to impaired sulfation of proteoglycans and cause spondyloepimetaphyseal dysplasia (SEMD) Pakistani type which is characterized by short stature, short bowed legs, platyspondyly, narrow intervertebral spaces, short femoral neck, irregular metaphyses, and epiphyses. The aim of this study was to describe the molecular, clinical, and endocrinological features of patients diagnosed with SEMD Pakistani type.

Seven patients from three families were evaluated. 5 patients from the first family (16y/M-33y/F-38y/F-34y/M-14y/M) had short stature (-5 SDS/-6 SDS/-6 SDS/-3.7 SDS/-2 SDS, respectively). A 33-year-old female patient had oligomenorrhea, hirsutism, and mildly elevated testosterone level after puberty and a 38-year-old female patient had infertility for 5 years. A 7-year-old girl from the second family suffered from back pain and short stature (-2SDS) and a 15-year-old girl from the third family had scoliosis and short stature (-5.45SDS).

All cases were clinically and radiologically compatible with SEMD Pakistani type. Plasma level of DHEAS was low in all patients. Homozygous c.1000C > T mutation was found in patients from the first and third families and compound heterozygote novel pathogenic c.639 + 1G > T and c.1000C > T mutations were found in a patient from the second family.

In conclusion, endocrinologic problems can be seen in patients with SEMD Pakistani type and patients should be monitored for these disorders.

(FC-06)

Clinical and Genetic Features of Our Patients with Hypophosphatemic Rickets

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While *PHEX* gene mutation is the most common form of inherited rickets, limited data exist regarding genetic etiology of hypophosphatemic rickets in Turkey. The aim of this study was to investigate the type of genetic defect in 16 index children and their families (12 unrelated, 1 related).

Following clinical and laboratory assessment, *PHEX* analysis was made initially unless a mutation in another gene was suspected. If negative, *FGF23*, *SLC34A3*, *SLC34A1*, *CYP27B1*, *VDR*, *DMP1*, and *ENPP1* genes were analyzed sequentially.

Following the investigation of index cases and their families, we identified 21 patients (16 children, 5 adults) diagnosed with hypophosphatemic rickets from 13 families. Nineteen of them (91%) had findings related with rickets and 12 (56%) had short stature. Calcium levels were normal, phosphorus low, ALP markedly elevated, and parathormone normal (n = 8, 38.1%) or mildly elevated (n = 13, 61.9%) in all patients. We found 10 different *PHEX* mutations in 17 (80.9%) patients, one novel SLC34A3 mutation in two siblings (9.5%), and no mutation in 2 patients (9.5%). Five *PHEX* mutations were *de novo*. Four novel *PHEX* mutations were: c.978_982dupCTACC (frameshift), c.1586 + 2T > G (splice site), c.436 + 1G > T (splice site), and c.1217G > T (p.C406F). Affected parents were all symptomatic but none were diagnosed previously.

The present study revealed that *PHEX* mutation seems to be the most prevalent mutation in Turkey as well. More attention should be paid to hypophosphatemia by the clinicians since some cases remain undiagnosed both during childhood and adulthood.

(FC-07)

The Relationship Between Gestational Diabetes Mellitus and Selenoprotein-P Plasma 1 *(SEPP1)* Gene Polymorphisms

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In this study, we aimed to investigate the relationship between *SEPP1* gene polymorphism and gestational diabetes mellitus (GDM).

The study included 40 patients with gestational diabetes mellitus (GDM group) and 40 healthy pregnant women (control group). Target single nucleotide polymorphisms (SNPs) were studied by using *rs4987017*, *rs13154178*, r*s146125471*, *rs28919926*, *rs16872762*, and TaqMan probes via ABI Prısm StepOnePlus Real Time System (Applied Biosystems, Foster City, CA).

rs4987017 gene polymorphism was found to be AA homozygous in all subjects in GDM and control groups. There was no significant difference in rs146125471, rs28919926, and rs16872762 polymorphisms between GDM and control groups ($p = 0.656$, $p = 0.30$, and $p = 0.627$, respectively). However, a significant difference was detected in rs13154178 polymorphism between the two groups ($p < 0.01$). In the control group, 61.5% of subjects were AA homozygous, while there was no AA homozygous patient in the GMD group. When mutants and AA homozygous patients were compared, fasting blood glucose and blood glucose level on hour one of 50 g OGTT were found to be significantly higher in patients with polymorphism than those without ($p < 0.001$ and $p = 0.01$, respectively). When effects of rs13154178 gene polymorphism on lipid levels were considered, it was found that LDL cholesterol, triglyceride, and total cholesterol levels were significantly lower in AA homozygous patients than in those carrying mutant gene ($p = 0.036$, $p = 0.009$, and $p = 0.006$, respectively).

To the best of our knowledge, this is the first study investigating *SEPP1* gene polymorphism in GDM. Our study suggests that rs13154178 gene polymorphism lead to predisposition to GDM in pregnant Turkish women.

(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

similar clinical features, but type 2 can be associated with mild intellectual disability. Type 3 (CAV1 mutation) is very rare, type 4 is the muscular type with pyloric stenosis, flat and striated muscle involvement, and serious arrhythmia. The index case has been followed until the age of 5.5 years, he had a pyloric stenosis operation and elevated CK as different from our three BSCL type 1 patients (5.5, 7.5, and 12-year-old). Interestingly, a Turkish child with BSCL and achalasia was reported with the same PTRF mutation. All of our patients had hypertriglyceridemia, hepatomegaly, and normal neuromotor development. Acanthosis nigricans, HCMP, enlarged hands and feet, and insulin resistance were present in 2 patients with AGPAT2 mutation.

A male infant, who had pyloric stenosis operation, was referred to our department because of developmental hip dysplasia, HCMP, and hepatomegaly. He had reduced adipose tissue, muscular hypertrophy, elevated CK values (1000 IU/L) and normal EMG results. The diagnosis was BSCL.

The identification of homozygous PTRF mutation verified the diagnosis of BSCL type 4.

Because insulin resistance has been described even in the infantile period, BSCL must come to mind in cases with pyloric stenosis and high CK values.

(FC-13)

Progeroid Syndrome Patients with ZMPSTE24 Deficiency Could Benefit When Treated with Rapamycin and Dimethylsulfoxide

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Patients with progeroid syndromes such as mandibuloacral dysplasia, type B (MADB) and restrictive dermopathy (RD) harbor mutations in zinc metalloproteinase (ZMPSTE24), an enzyme essential for posttranslational proteolysis of prelamin A to form mature lamin A. Dermal fibroblasts from these patients show increased nuclear dysmorphology and reduced proliferation; however, the efficacy of various pharmacological agents in reversing these cellular phenotypes remains unknown.

In this study, fibroblasts from MADB patients exhibited marked nuclear abnormalities and reduced proliferation that improved upon treatment with rapamycin and dimethylsulfoxide but not with other agents, including farnesyl transferase inhibitors.

Surprisingly, fibroblasts from an RD patient with a homozygous null mutation in ZMPSTE24, resulting in exclusive accumulation of prelamin A with no lamin A on immunoblotting of cellular lysate, exhibited few nuclear abnormalities and near-normal cellular proliferation. An unbiased proteomic analysis of the cellular lysate from RD fibroblasts revealed a lack of processing of vimentin, a cytoskeletal protein. Interestingly, the assembly of vimentin microfibrils in MADB fibroblasts improved with rapamycin and dimethylsulfoxide.

We conclude that rapamycin and dimethylsulfoxide are beneficial for improving nuclear morphology and cell proliferation of MADB fibroblasts. Data from RD fibroblasts also suggest that prelamin A accumulation by itself might not be detrimental and requires additional alterations at the cellular level to manifest the phenotype.