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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.

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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 (10th-25th centile), 74 cm (3th-10th centile), and 43 cm (<3th 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.

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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 adrenocorticotrophic 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.

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***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.

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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*