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EDİTÖRE MEKTUP / LETTER TO THE EDITOR

A newborn case diagnosed as isolated TBX1 deletion with 22q11 deletion syndrome

İzole TB delesyonu saptanan 22q11 delesyon sendromlu bir yenidoğan olgusu

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To the Editor,

22q11 deletion syndrome is a heterogeneous disease group that the clinical findings may be seen depending on penetrance deficiency, variable expressivity and deletion size[1]. While around of 90% of cases consists of the classical type 22q11 deletion syndrome developed in size of 3 megabase (Mb) deletion, 1.5 Mb deletion exists in 7% and smaller deletions in remaining part. This deletion region usually contains ~35 genes. *TBX1* gene mutations are stated in some of the cases no deletion is diagnosed. Although it presents with conotruncal heart anomalies, thymus and parathyroid hypoplasia, dysmorphic findings, cleft palate and learning disability, clinical signs are quite variable[2]. Here, we present a newborn case of prenatally detected scoliosis and postnatally diagnosed hypocalcemia, pulmonary hypertension, hemivertebra, costal anomaly and isolated *TBX1* gene deletion with 22q11 deletion syndrome.

A 27-year-old, gravida 2 mother delivered a male baby at 38 of weeks gestation by cesarean section, with a birth weight of 2910 g. Parents were not consanguineus. Scoliosis was detected on the antenatal ultrasonography. He was intubated and started mechanically ventilation due to respiratory failure. He was given intra venous calcium gluconate therapy because of hypocalcemia. Pulmonary hypertension was detected on 13 day of life on the transthorasic echocardiography but structural anomalies were not noted. The patient whose pulmonary artery pressure was 60 mmHg was referred to our hospital. Thorax tomography angiography findings were follows: main pulmonary artery and branches were patent, no apparent thromboembolism was available, cardiomegaly was present. Patent ductus arteriosus(wide), pulmonary hypertension, tricuspid and mitral insufficiency were diagnosed in repeated echocardiography. Chest radiography revealed nine costas on the right lung and ten costas on the left lung. Hemivertebra anomaly was diagnosed in L1 vertebra corpus and the butterfly vertebra and hemivertebra in thoracic vertebras in vertebra graphies. Scoliotic curve whose convexity looks towards left was noted. Pedigree analysis revealed no abnormality. Karyotype analysis showed 46, XY. *TBX1* gene deletion was diagnosed [rsa 22q11(*TBX1*)x1] by Multiplex Ligation-dependent Probe Amplification (MLPA) DiGeorge probe set (P250-B1 DiGeorge, MRC-Holland, Amsterdam, the Netherlands) (Fig 1).

Anthropometric measurements in 8th month of the patient were compatible with that of 4th month. Body weight is measured in 5 kg (<3P), length in 62 cm (<3P). He is still on follow up in our patient clinic with no neurologic deficits. He had recurrent upper respiratory tract infection.

Informed written consent of the patient was obtained for publication.

Haploinsufficiency, gain of function and mutation of *TBX1* gene are kept responsible for cleft palate,

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hypocalcemia, thymus hypoplasia, cardiac anomalies and face appearance being typical or atypical for 22q11 deletion syndrome[2]. No relationship with mental retardation and learning disability was detected. However, the relationship with psychiatric problems seen in Velocardiofacial Syndrome (OMIM#192430) and DiGeorge Syndrome (OMIM#188400) is reported. Our patient, a newborn with neonatal hypocalcemia, pulmonary hypertension and costovertebral anomalies but no typical face findings, cleft palate and structural cardiac anomaly

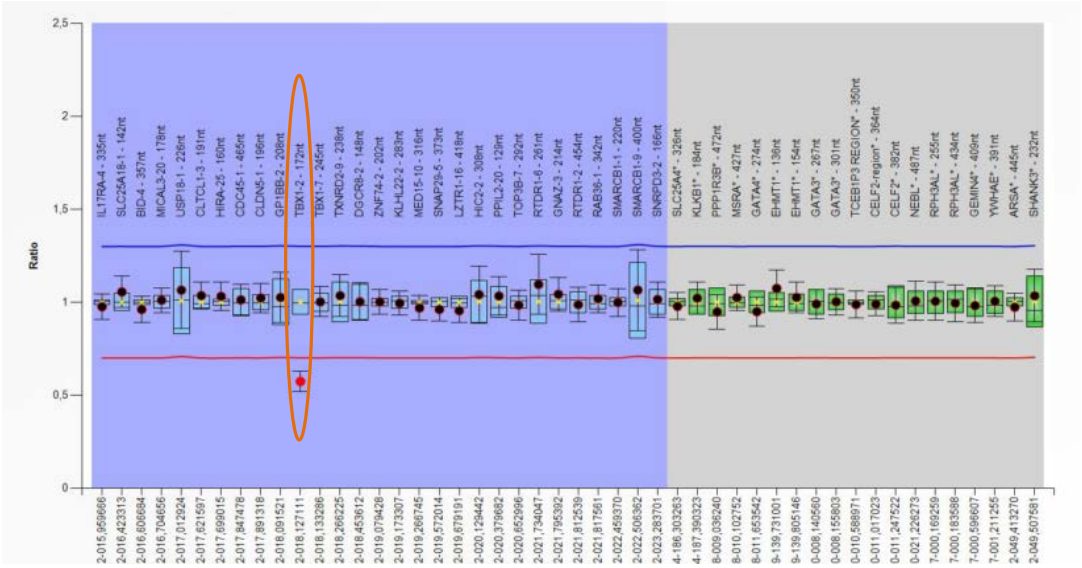

Figure 1. Heterozygote deletion was showed in *TBX1* gene with SALSA MLPA P0250-B1 kit.

Scoliosis has been reported to be present in 47% of the patients with 22q11 deletion syndrome. During the evaluation conducted due to the scoliosis diagnosed in prenatal follow-up, it was diagnosed that nine costas on the right lung, hemivertebra and butterfly vertebra anomalies in thoracic vertebras and hemivertebra anomaly in L1 vertebra corpus were available. We demonstrate isolated *TBX1* gene deletion by 22qdel MLPA our patient. *TBX1* gene is a member of T-box gene family responsible for arrangement of embryonic developmental process. Previous studies reported that *TBX1* gene is related to cardiovascular, thymic, parathyroid, palatal and dental development[2]. Besides, it was shown that it is expressed in vertebra and tooth bud[3]. Funato et al. has demonstrated that *TBX1* expression is required from normal skeleton development and the mesoderm and crista neuralis based osteoblast alteration[3]. Our findings also support that *TBX1* gene plays role in development of vertebras and costas. Therefore, evaluation of vertebra and costas for the patients *TBX1* mutation is diagnosed or searching *TBX1* gene mutations in case of spinal costal anomaly is significant.

The relationship between *TBX1* and cardiac anomalies is controversial[4]. Recently, due to heterogeneous phenotypes associated with *TBX1*, in the development of cardiac abnormalities, it is thought to play a role in interactions with other regulatory genes of TBX1 gene. No structural heart anomaly was diagnosed in our patient. Non-observing heart outlet anomalies which are frequently encountered in 22qdel syndromes also support this opinion.

In a study performed on mice, it is demonstrated that craniofacial impact of *TBX1* gene is modified by *CHRD* (Cordin: 603475) gene. It is determined that isolated hypomorphic *TBX1* mutations decreases penetrance from the aspect of craniofacial findings at the lack of *CHRD* mutation[5]. *TBX1* gene deletion is a mutation with hypomorphic effect. In our patient, the reason for failing to detect dysmorphic findings may be modification of *TBX1* gene by other genes.

In similar to our patient, *TBX1* gene deletion may present atypical 22q11 deletion syndrome with costovertebral anomaly. In the patients that G-band chromosome analysis and FISH methods could not diagnose, *TBX1* gene mutations or copy number variations should be search. In addition, adjacent or regulatory other genes should also be assessed. To that end, use of molecular methods such as MLPA, array Comperatif Genomic Hybridization (aCGH) and exom sequencing will assist detection of valuable findings in terms of understanding phenotype-genotype relationship as well as this syndrome showing clinical heterogeneity.

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