CASE REPORT / OLGU SUNUMU

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Kromozom 3 Dengesizliği Olan Bir Olgunun Genotip Fenotip Korelasyonu

Genotype Phenotype Correlation of A Case Having Chromosome 3 Imbalance

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Abstract

We report a boy carrying a recombinant chromosome 3, with deletion of 6.2 Mb from 3p26.3 to 3p26.1 and a duplication of 18.7 Mb from 3q26.33 to 3q29, resulting from a maternal pericentric inversion of the chromosome 3. He had delayed development, dysmorphic facial features, strabismus, hirsutism, and he was operated for ventricular septal defect. Furthermore, we discuss genotype-phenotype correlation with similar cases reported in the literature.

Key Words: Duplication of 3q, Deletion of 3p, Chromosomal Rearrangements

Öz

Maternal 3. kromozomdaki perisentrik inversiyon nedeniyle ortaya çıkan, 3p26.3-3p26.1 bölgesinde 6.2 Mb boyutunda delesyon, 3q26.33-3q29 bölgesinde ise 18.7 Mb boyutunda duplikasyona sahip rekombinant bir üçüncü kromozom taşıyan ve gelişme geriliği, dismorfik yüz bulguları, strabismus, hirşutizm ile birlikte ventriküler septal defekt nedeniyle operasyon öyküsü bulunan bir olguyu literatürde bildirilen benzer olgular ile genotip-fenotip korelasyonu yaparak sunuyoruz.

Anahtar Kelimeler: 3q Duplikasyonu, 3p Delesyonu, Kromozomal Yeniden Düzenlenmeler

Introduction

Partial duplication of 3q (3q+) and partial deletion of 3p (3p-) syndromes are rare, but clinically recognizable conditions. It has been shown to emerge from the meiotic recombination of the 3rd chromosome containing a pericentric inversion in one of the parents (1). 3q+ syndrome that resembles Cornelia de Lange syndrome, represents one or many of the features such as mental retardation, developmental delay, seizures, prominent eyelashes, down-slanting palpebral fissures, epicanthal folds, broad nose, low-set malformed ears, prominent philtrum, down-turned corners of the mouth and digital anomalies including brachydactyly and clinodactyly, hypertrichosis, cardiac, renal, and genital malformations in addition to pre- and postnatal growth retardation (2). More rarely reported features contain ocular anomalies, conductive hearing loss and hip dysplasia (3). Almost one-third of the patients pass away within the first year of life owing to infections or cardiac anomalies (4).

On the other hand, 3p- syndrome is a rare contiguous gene syndrome which is caused by 200 kb to 12.5 Mb deletions in 3pter-p25 region with a wide clinical spectrum such as psychomotor delay, growth retardation, congenital heart defects especially atrioventricular septal defects and dysmorphic findings including synophrys, epicanthic folds, ptosis, down-slanting palpebral fissures, broad nose, low-set ears, long philtrum, down-turned mouth, and micrognathia, hypertrichosis

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(5). In addition to above findings, cleft palate, preauricular pits, renal anomalies, sacral dimple, gastrointestinal anomalies and postaxial polydactyly occur variably (6). Symptoms and severity of the conditions may vary due to the genes content of the deleted region. Here, we present a case with a 3p26.3-p26.1 deletion in combination with the 3q26-q29 duplication. The clinical presentation of dup(3q)/del(3p) is discussed as well.

Case Report

The patient, a three and a half-year-old boy, was born at gestational age of 36 weeks due to preterm labor by cesarean section after an uncomplicated pregnancy with a birth weight of 2,700 g. He is the third child of a healthy third-degree consanguineous couple. Mother had four first trimester abortions. The neonatal history of the patient was uneventful; his psychomotor milestones were delayed as he sat unsupported at the age of two and walked unaided at 3.5 years of age. He was referred to us because of his developmental delay, dysmorphic features such as synophrys, strabismus, long-curly eyelashes, up-slanting palpebral fissures, bulbous and short nose, posteriorly rotated and low-set ears, prominent philtrum, hypertrichosis, pectus excavatum, bilateral hallux valgus, fourth-fifth finger clinodactyly of feet, overlapped foot fingers (Figure 1). The patient presented with speech and motor developmental delays. His height was 95 cm (10-25p), whereas weight and head circumference were 16 kg (50-75p) and 50 cm (25-50p), respectively. He was operated for ventricular septal defect (VSD). Magnetic resonance imaging of the brain was performed at the age of 3 and showed mild enlargement in lateral ventricles. Abdominal ultrasonography was normal. Visual and hearing examinations were normal. Laboratory findings for metabolic disorders were negative.

Written informed consent was obtained from patient's legal guardians. Peripheral blood lymphocyte culture followed by metaphase preparation was performed according to standard protocols. Twenty metaphases were analyzed with 550-band- level by GTG banding technique. Fluorescence in situ hybridisation (FISH) analysis was carried out using subtelomeric probes (Kreatech, Amsterdam, Netherlands) for chromosome 3. Both the conventional cytogenetics and FISH results were described according to ISCN (2016). For molecular karyotyping, genomic DNA was isolated from peripheral blood sample using MagnaPure LC DNA Isolation Kit Large Volume and MagnaPure LC Instrument (Roche Applied Science Mannheim, Germany). In order to specify the breakpoints and better identify the recombinant chromosome, chromosomal microarray analyses (CMA) was performed [Affymetrix Cytoscan Optima Chips, Waltham, MA USA (hg19)].

Karyotype analysis revealed a structural abnormality as 46,XY,add(3)(p26) (Figure 2a). FISH analysis with subtelomeric regions of chromosome 3 showed a deletion on the short arm and a duplicated subtelomeric region of the long arm of chromosome 3 located on distal 3p (Figure 2c). We checked for parental transmission and found out a maternal pericentric inversion (Figure 2b), the father's karyotype was normal. Patient's karyotype was 46,XY, rec(3)dup(3)(q?q26.1),inv(3)(p26q26.1)mat[20].ish rec(3)inv(3)(p26)(D3S4558-,D3S4168+)(q26.1)(D3S4168+). In order to define exact size of the chromosomal anomaly and the involved genes in these regions, CMA was performed. CMA revealed a 6,2 Mb loss at 3p26.3p26.1 (chr3:61,891-6,306,332) and a 18,7 Mb gain at 3q26.33q29 (chr3:179,134,633-197,851,986) (Figure 2d). Final karyotype of patient was 46,XY,rec(3)dup(3q)inv(3)(p26q26.1)mat.arr 3p26.3p26.1(61,891_6,306,332)x1,3q26.3 3q29(179,134,633_197,851,986)x3.

Discussion

Most cases with 3q duplication appear to be the result of an unbalanced translocation or inversion resulting in an associated deletion of another chromosomal segment, as in our patient (2). After pairing in a pericentric inversion generates four products: Chromosome with normal gene order, chromosome with inverted gene order and two duplication and/or deletion products in which one or more loci are duplicated or deleted, depending on where the crossover occurs (7). The phenotype is quite variable depending on the size of the duplicated/deleted segments. In this case the duplicated region contains 18.7Mb of genomic information and 110 OMIM (https://www.ncbi.nlm.nih.gov/omim) genes. A female patient who had low-set ears, high arched palate, developmental delay, speech defects, hirsutism, heart, hand and foot anomalies, umbilical hernia with an

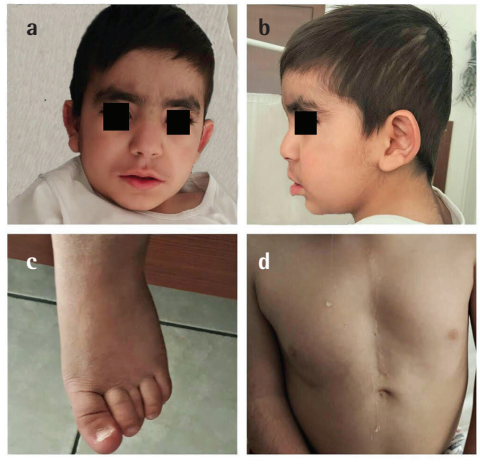

Figure 1 a–d: Dysmorphic appearance and skelatal findings of the patient. Note: a) Synophrys, strabismus, long-curly eyelashes, up-slanting palpebral fissures, bulbous and short nose, prominent philtrum. b) Posteriorly rotated and low-set ears, hypertrichosis. c) Hallux valgus, fourth-fifth finger clinodactyly of foot and overlapped foot fingers. d) Pectus excavatum

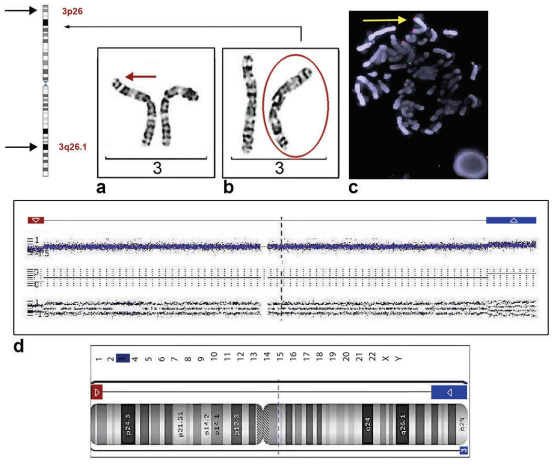

Figure 2 a–d: a) Chr.3 of patient. 46,XY,add(3)(p26) (left) b) Chr.3 of patient's mother. (right) 46,XX,inv(3)(p26;q26.1) Note: Broken regions were indicated with an black arrow on the ideogram. c) FISH analysis of proband. Arrowhead shows recombinant chromosome with a deletion on the short arm and a duplicated subtelomeric region of the long arm of chromosome 3 which is located on distal 3p (spectrum green: D3S4558, 3p; spectrum red: D3S4168,3q, Kreatech) d) Array CGH analysis. Note: 6,2Mb loss at 3p26.3p26.1 and 18,7Mb gain at 3q26.33q29 (Red signal deletion, blue signal duplication) (CytoScanOptima_Array)

FISH: Fluorescence in situ hybridization, CGH: Comparative genomic hybridization

almost similar amplified region due to a marker chromosome on 3q26.32-q29 was reported by Cunha et al. (8). All these findings were present in our patient except umbilical hernia. The review of the literature revealed that developmental delay/intellectual disability, bushy eyebrows, long eyelashes, anteverted nostrils, downturned corners of the mouth were observed in pure 3q duplication cases encompassing the 3q26.33-q29 region, like in our case (9,10). Common clinical findings are microcephaly, downturned corners of mouth and abnormality of the pinna in patients in DECIPHER database (http://decipher.sanger.ac.uk/) with gains in the region close the presented case (DECIPHER patient numbers used: 392621, 393053, 392048). However, our patient did not have microcephaly and pinna abnormality.

Similar cases depicted from the literature are presented in Table 1 with putative loci associations and phenotypic findings.

Ireland et al. (11) suggested 3q26.3 as a critical region, and subsequently the proposed critical region for trisomy 3q was narrowed to 3q26.3-3q27 by Aqua et al. (12). Latterly, minimal region of duplication overlap was suggested to be at 3q29 (13). Duplication of 3q26.33-q29 in our proband overlaps with these specified critical regions of 3q duplication syndrome, however this case is unique with respect to the genotype content, that does not exist in the literature to the best of our knowledge. Furthermore, our case had an 18.7Mb duplicated region of 3q26.33-q29 encompassing *CLDN1* (MIM 603718) and *CLDN16* (MIM 603959) genes, located on 3q28. Mutations of these genes are associated with multiple congenital anomalies such as atrial septal defect, VSD, hypertrichosis (14). The possible gene dosage effect of these genes could have caused the phenotype in our proband. According to Rodríguez et al. (15), *DVL3* (MIM 601368) gene might be the candidate gene for the VSD. *ACTL6* (MIM 604958) gene on chr3q26.33 and *FGF12* (MIM 601513) gene on chr3q28-q29 play a role in the neural growth processes (15). *FGF12* gene, a member of the fibroblast growth factor gene family, is expressed primarily in the nervous system and play a role in cerebral development. The proband also had duplicated *SOX2* (MIM 184429) located on 3q26.33, which is expressed in high levels in embryonic and fetal human brain and is tightly related to neuronal differentiation (16). Neurological deficits and ocular anomalies such as anophthalmia or microphthalmia have been reported in cases with loss of function in the *SOX2* gene. On the other hand, duplications encompassing *SOX2* gene are not thought to cause structural eye defects but are associated with other features of *SOX2* disorder such as developmental delay, motor delay, intellectual disability, hypotonia (https://www.deciphergenomics.org). In accordance with the literature, the proband had no ocular findings, but his psychomotor delay could be attributed to the copy number change in the *SOX2* gene. The *EIF2B5* (MIM 603945) and *ALG3* (MIM 608750) genes on chromosome 3q27.1 associated with neuronal development and facial dysmorphism (17). His developmental disability might also be attributable to a gain of *EIF2B5*, *ALG3* copy number. Another gene, *IGF2BP2* (MIM 608289) located on 3q27.2 is associated with over-growth, encodes a member of the *IGF2* mRNA-binding protein family regulating *IGF2* hormone effects on pre-postnatal growth (18). Although this gene is duplicated in proband, excessive growth, as described in the other reports, were not found in our examination. Mills et al. (19) suggested that limb anomalies may be associated with loss of function in the *TP63* (MIM 603273) gene on chromosome 3q28 that is essential for limb formation. In our opinion, his clinodactyly and overlapping toes might be ascribable to *TP63* copy number.

The deleted region at 3p26.3p26.1 in the case encompasses 12 OMIM genes including *CRBN* (MIM 609262), *CNTN4* (MIM 607280), *ITPR1* (MIM 147265), *SUMF1* (MIM 607939) which were reported as potential candidate genes in 3p- phenotype (5). Although intellectual disabilities are almost any time associated with large size of 3p deletions, mild abnormalities have been described rarely in patients with a 3p25-p26 deletion (6). A number of genes as *CHL1* (CALL) on 3p26.3, *ITPR1* on 3p26.1 have been implicated in the pathogenesis of intellectual disability associated with 3p- syndrome (20). *CNTN6* (MIM 607220) and *CHL1* (MIM 607416) that has been included in neuronal development are located in deleted region. *CHL1* was suggested as a candidate gene for non-specific learning disability (21). Loss of these genes could have caused proband's psychomotor development delay. *CNTN4* gene which is located at 3p26.3 (belonging to the same family as *CNTN6* gene located

Table 1: Similar cases from the literature and suggested gene associations

3q duplication phenotype	Our case	Probable associations	Encoded protein	Functions	References
Cardiac defects	ASD/ VSD	*CLDN1* (MIM 603718)	Claudin 1	Epithelial or endothelial cell-to-cell adhesion tight junction proteins	Türkmen et al. (14)
		CLDN16 (MIM 603959)	Claudin 16		
	VSD	*DVL3* (MIM 601368)	Disheveled segment polarity protein 3	Involved in the signal transduction pathway mediated by multiple Wnt genes.	Rodríguez et al. (15)
Hypertrichosis/ Hirsutism	+	*CLDN1*	Claudin 1	Epithelial or endothelial cell-to-cell adhesion tight junction proteins	Türkmen et al. (14)
		CLDN16	Claudin 16		
Facial dysmorphism	+	*EIF2B5* (MIM 603945)	eIF2B	A heteropentameric guanine nucleotide exchange factor necessary for the proper function of the translation initiation factor eIF2	Dietrich et al. (17)
		ALG3 (MIM 608750)	ALG3 family	Catalyses the addition of the first dol-P-Man derived mannose in an alpha 1,3 linkage to Man5GlcNAc2-PP-Dol	Dietrich et al. (17)
		TP63 (MIM 603273)	Tumor protein p63	Epidermal cell division, epithelial cell development, keratinocyte differentiation and proliferation and essential for limb formation	Mills et al. (19), Cunha et al. (8)
Clinodactyly	+	*TP63*	Tumor protein p63		
3p deletion phenotype					
Intellectual disability	+	*CHL1 (CALL)* (MIM 607416)	Neural cell adhesion molecule L1-like protein	Extracellular matrix and cell adhesion protein that plays a role in nervous system development and in synaptic plasticity	Higgins et al. (20)
		ITPR1 (MIM 147265)	Inositol 1,4,5-trisphosphate receptor type 1	Intracellular channel that mediates calcium release from the endoplasmic reticulum	

VSD: Ventricular septal defect, ASD: Atrial septal defect

on 3p26.3) was disrupted in a case with mental retardation reported by Fernandez et al. (22). In our opinion, *CNTN6* might be a significant gene in brain development and might be associated with proband's mental condition. Shuib et al. (6) suggested that loss of *CNTN4* (contactin 4), that encodes a GPI-anchored neuronal membrane protein that functions as a cell adhesion molecule, is not sufficient to cause a 3p- syndrome clinic but, in combination with other autistic susceptibility alleles, could contribute to autistic spectrum disorder. Homozygous mutations of *CRBN* gene have been shown in a patient with intellectual disability (23). Multiple sulfatase deficiency (MSD) is caused by biallelic mutation in the *SUMF1* gene. In a study, it has been observed that *SUMF1*-null mice showed growth retardation, skeletal abnormalities, and neurologic deficits (24). Since the deletion of these genes was mono-allelic in our patient, although sequence analysis could not be performed for the second allele of the *SUMF1* and *CRBN* genes, the phenotype of the proband was not associated with *MSD*.

In 3p- syndrome, 3p25 is a critical region for heart diseases and four candidate genes have been suggested: *ATG7* (MIM 608760), *HRH1* (MIM 600167), *SLC6A1* (MIM 137165), *CRELD1* (MIM 607170). However, this region is not deleted in the proband. We suggest that congenital cardiac defects in our case (VSD) result from 3q26.3-q29 duplication (25).

Similar cases with pure deletion including the region 3p26.1-26.3 in DECIPHER shows that intellectual disability, long philtrum, low-set ears were common findings. Although our patient did not have long philtrum, this can be explained by the size of the deleted region or the affected genes, or it may be related to the duplicated region complicating the phenotype. Moreover, developmental delay, hirsutism, and gastroesophageal reflux (GER) have been noted in a case with an almost similar gain and loss to our case (https://www.deciphergenomics.org). However, our proband does not have GER complaints.

Conclusion

Taken together, the clinical findings of our case were more consistent with the 3q duplication phenotype than the 3p deletion. On the other hand, establishing a genotype-phenotype correlation and delineating the genes in the deletion/duplication segment which lead to more prominent features for this syndrome is difficult. The accumulation of the mapping data would eventually provide a well-rounded information for the genetic counselling of this syndrome.

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Ethics

Informed Consent: Informed consent was obtained from the patients and/or their family/legal guardians.

Peer-reviewed: Externally peer-reviewed.

Authorship Contributions

Data Collection or Processing: E.T., E.G.İ., Ş.A., A.C.C., Analysis or Interpretation: E.T., E.G.İ., Ş.A., A.C.C., T.T., Literature Search: E.T., Writing: E.T., T.T.

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