IJCMBS

THE INTERNATIONAL JOURNAL OF CURRENT MEDICAL AND BIOLOGICAL SCIENCES e-ISSN: 2791-8815

Orgınal Article

Newly defined unbalanced distributions of paternal balanced chromosomal translocation and review of the literature

Paternal dengeli kromozomal translokasyonun yeni tanımlanan Dengesiz dağılımları ve literatürün gözden geçirilmesi

Senol Citli[1*]

[1] Department of Medical Genetics, Recep Tayyip Erdogan University Medical Faculty, Rize, / TURKİYE

Corresponding author:
Dr. Şenol Çitli
Adress:
Department of Medical Genetics, Recep Tayyip Erdogan University Medical Faculty, Rize, TURKİYE
E-mail: drsenolcitli@gmail.com
Received: 27.09.2022
Accepted: 14.10.2022
Cite as: Citli.S. Newly defined Unbalanced distributions of paternal balanced chromosomal translocation and review of the literatureIJCMBS 2022;2(3):171-178 doi.org/ 10.5281/zenodo.7199890

Highlights

-It is common for individuals with balanced chromosomal translocations to show unbalanced chromosomal distribution in meiotic segregation.
- Coexistences of 5p partial trisomy with 7q partial monosomy and 5p partial monosomy with 7q partial trisomy in children due to balanced translocation of chromosomes 5 and 7 in their parent have not been reported before.
-It can be said that most of the deletion or duplication cases of 7q or 5p defined individually in the literature have milder clinic severity than our cases. This may indicate that by increase in the number and size of the affected chromosome regions, the clinic appearance would be severe.
-Copy Number Variation (CNV) analysis by microarray is important in the diagnosis of congenital anomalies, especially in motor-mental retardation and can identify new microdeletions or microduplications.

Abstract

Background: Balanced chromosomal re-arrangements (BCR) are re-arrangements with no loss or gain of genetic material and usually not associated with clinical abnormalities. However, BCR carriers may have children with a chromosomal anomaly as a result of an unbalanced transfer of chromosomes to the offsprings. The children with unbalanced chromosomal translocations may exhibit many congenital anomalies, especially motor-mental retardasyon. We report unbalanced translocation and multiple congenital anomalies in two siblings. Chromosomal microarray analysis was performed on the both siblings using Agilent Oligonucleotide Microarray 8×60K. Chromosomal microarray analysis showed partial deletion in 5p and partial duplication in 7q (arr[GRCh37] 5p15.33-p15.2x1, 7q36.1-q36.3x3) in one sibling, and partial duplication in 5p and partial deletion in 7q (arr[GRCh37] 5p15.33-p15.2x3, 7q36.1-q36.3x1) in the other sibling were detected. Subtelomeric Fluorescent In Situ Hybridization (FISH) analysis was performed on the entire family using Cytocell Telomark Probe. The father was found to have 46,XY.ish t(5;7)(p15-,q36+;q36-,p15+) balanced chromosomal translocation structure, while the mother was found to have 46,XX normal chromosome structure. To the best of our knowledge, 5p partial trisomy+7q partial monosomy and 5p partial monosomy+7q partial trisomy have not been previously reported. These findings provide us with the conclusion that Copy Number Variation (CNV) analysis with microarray is important in the diagnosis of congenital anomalies, especially motor-mental retardation.
Keywords: Chromosomal rearrangement, Congenital anomaly, Microarray, Unbalanced translocation

ÖZ

Dengeli kromozomal yeniden düzenlemeler (BCR), genetik materyal kaybı veya kazanımı olmayan ve genellikle klinik anormalliklerle ilişkili olmayan yeniden düzenlemelerdir. Bununla birlikte, BCR taşıyıcıları, kromozomların yavrulara dengesiz aktarımı sonucu olarak kromozom anomalili çocuklara sahip olabilir. Dengesiz kromozomal translokasyonlu çocuklar başta motor-mental retardasyon olmak üzere birçok konjenital anomali gösterebilirler. İki kardeşte dengesiz translokasyon ve çoklu konjenital anomalileri rapor ediyoruz. Agilent Oligonucleotide Microarray 8×60K kullanılarak her iki kardeş üzerinde kromozomal mikroarray analizi yapıldı. Kromozomal mikroarray analizinde çocukların birinde 5p de parsiyel delesyon ve 7q da parsiyel duplikasyon (arr[GRCh37] 5p15.33-p15.2x1, 7q36.1-q36.3x3) saptanırken diğer çocukta 5p de parsiyel duplikasyon ve 7q da parsiyel delesyon (arr[GRCh37] 5p15.33-p15.2x3, 7q36.1-q36.3x1) saptandı. Tüm aile üzerinde Cytocell Telomark Probe kullanılarak Subtelomeric Fluorescent In Situ Hybridization (FISH) analizi yapıldı. Babanın 46, XY.ish t(5;7) (p15-,q36+;q36-,p15+) dengeli kromozomal translokasyon yapısına sahip olduğu, annenin ise 46,XX normal kromozom yapısına sahip olduğu belirlendi. Mevcut bilgilerimize göre 5p parsiyel trizomizisi + 7q parsiyel monozomisi ve 5p parsiyel monozomisi + 7q parsiyel trizomisi daha önce raporlanmamıştır. Bu bulgular bize, motor-mental retardasyon başta olmak üzere konjenital anomalilerin tanısında mikroarray ile kopya sayısı varyasyon analizinin önemli olduğu sonucunu vermektedir.

Anahtar kelimeler: Kromozomal yeniden düzenleme, Konjenital anomali, Mikroarray, Dengesiz Translokasyon

Introduction

In humans, the incidence of balanced chromosomal translocation is approximately 1/500 (1, 2). Balanced chromosomal translocations are re-arrangements with no loss of genetic material or gain. Most balanced chromosomal re-arrangements (BCR) are not considered to be associated with clinical abnormalities or an abnormal phenotype (3). However, BCR carriers are alarming as they are riskier in terms of recurrent pregnancy losses and congenital anomalies in offsprings. It is estimated that 6.7% of de novo BCR carriers have a risk of phenotypic abnormality (4). Most of the hypotheses proposed to explain the relationship of BCRs with phenotypic abnormalities include monogenic disorders such as sickle cell anemia caused by modification or disruption of genes in the re-arrangement region at the molecular level, the mosaic structure containing unbalanced re-arrangement in different tissues, uniparental disomy of one of the chromosomes in the re-arrangement, and situations such as position effect variation phenomenon (1, 5).

Reciprocal translocations are structural chromosomal rearrangements in which two chromosomes break and mutual exchange of distal chromosomal segments occur, and two new derivative chromosomes are formed without loss or gain of genetic material. These balanced translocations typically do not produce a significant phenotypic effect unless one or both of the chromosomal breakpoints contain an important functional gene. However, 2:2 segregation may occur during the meiotic division, which leads to the formation of gametes, which are partially disomic for a chromosomal segment and partially nullisomic for the other. This results in a combination of partial trisomy and partial monosomy in the zygote (6).

In this article, two boys with unbalanced translocation and multiple congenital anomalies of a father with a balanced chromosomal translocation of 46,XY.ish t(5;7)(p15-,q36+;q36-,p15+)(5pter-,7qter+;7qter-,5pter+) and a mother with a 46,XX normal chromosome structure were presented. Partial deletion in 5p and partial duplication in 7q (arr[GRCh37] 5p15.33-p15.2x1, 7q36.1-q36.3x3) in one sibling, and partial duplication in 5p and partial deletion in 7q (arr[GRCh37] 5p15.33-p15.2x3, 7q36.1-q36.3x1) in the other sibling were detected.

Material and Methods:

Detailed anamnesis of the patients was obtained and physical examinations were performed according to the guidelines (7, 8). In all cases, chromosome analysis was performed in lymphocyte culture from peripheral blood samples. Following Trypsin-Giemsa (GTG) banding, twenty metaphases in each sample were routinely analyzed at 550 band level. Reporting was made according to the guidelines of the International Human Cytogenetic Nomenclature System (ISCN) 2016. The FISH analyses were performed using the Cytocell Telomark probe. Subtelomere multicolor DNA probe Mix 05 (5p Green, 5q Orange) and Mix 07 (7p Green, 7q Orange, 14q Orange and Green, TCARD (14q112) (blue) (Cytocell Ltd. Cambridge, UK) were used to identify subtelomeric rearrangements. About ten metaphases were captured under the Zeiss Axioscope.A1 microscope (Germany) and analyzed with Argenit Chromosome Analysis System (AKAS) (İstanbul, Turkey). The microarray analysis was performed using Agilent Oligonucleotide Microarray 8×60K microarrays platform and results were analyzed using CytoGenomics software, Edition 5.0.1.6. (Agilent Technologies, Santa Clara, CA).

The parents of children gave written consent for all genetic testing and for the academical use of patient photographs.

Results

Case 1

Proband was a 9-year-old boy born from a couple who was not related but from the same village and was directed to us for severe intellectual-motor disability. The patient was born with the C/S (due to fetal bradycardia) at 41 weeks of gestation from the first pregnancy of the 19-year-old mother. His birth weight was 3250 g. He was hypoactive at birth and had incubator care for 1 week postnatally. He achieved head control at the 9th month of age, sitting with support at the 7-8th month and sitting without support at the 10th month. He never walked and talked. At the age of 7, his scoliosis appeared. On physical examination, spelling was available, but the skill of forming words and sentences was not developed. He knew his mother but described his wishes in angrily. There were no involuntary movements, but autistic behaviors. He displayed behaviors of hitting/hurting himself. His height was 121 cm (<3 p.), weight 19 kg (<3 p.), and head circumference 48 cm (<3 p.). He could hold an object with his hand. There was one hypopigmented and one 2x2 cm hyperpigmented Cafe Au Lait. There were dysmorphic findings such as microcephaly, an outward shift in the left eye, long

palpebral fissures, dental anomalies, postaxial polydactyly of left foot, operated bilateral cryptorchidism (Figure 1). He had teeth grinding and stereotype. He could not receive simple commands. Deep tendon reflexes were alive. There was no pathological reflex. He was walking with support but could not speak. In cranial MRI, there was mildly dysmorphic cerebellar sulcus, bilateral slight pachygyria in temporal gyri, mild hypoplasia in inferior cerebellar vermis (Figure 2). No pathology was detected in echocardiography.

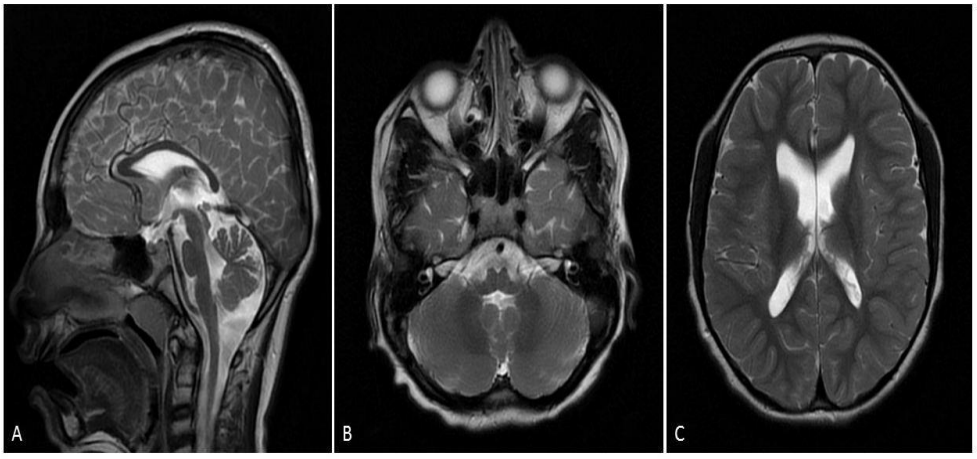

Figure 2. 9-year-old male. A) Hypoplasia of brain stem compartments and corpus callosum on the sagittal T2-weighted image. **B**) Normal cerebellum on the axial T2-weighted image. **C**) Slight dilatation of the lateral ventricles on the axial T2-weighted image.

In the chromosome analysis of the patient's peripheral blood by G-banding after short-term cell culture, the derivative structure of the short (p) arm of chromosome 5 was observed. After the chromosome analysis of the parents, the normal chromosome structure of 46, XX was observed in the mother, while a balanced reciprocal translocation was detected between the chromosome regions 5p15 and 7q36 (46,XY.ish t(5;7)(p15-,q36+;q36-,p15+)) in the father. As a result of the unbalanced transfer of this translocation to the child, it was observed that chromosome 5 had a deletion from the p15 region to the terminal, and the part of chromosome 7 from the q36 region to the terminal was translocated to this region. Accordingly, partial monosomy of chromosome 5 and partial trisomy of chromosome 7 were observed. These results were confirmed with the subtelomeric FISH analysis (46,XY.ish der(5)t(5;7)(p15-;q36+)(5pter-;7qter+)pat).
In the microarray analysis, 14.422.009 kb loss (number of markers: 294) covering the 5p15.33-p15.2 region (57 entries in OMIM Gene Map, 23 of which are phenotype related), and 8,645,736 kb gain (number of markers: 263) covering the 7q36.1-q36.3 region (61 entries in OMIM Gene Map, 27 of which are phenotype related) were detected (arr[GRCh37] 5p15.33-p15.2 (20,149-14,444,157)x1, 7q36.1-q36.3 (150,482,821-159,128,556)x3) (Figure 1).

Case 2

The second brother was an 8-year-old boy born from the second pregnancy of the 20-year-old mother by C/S at 41 weeks of gestation and weighing 2000 g. He had a history of intrauterine growth retardation, green vomiting at and after birth, and postnatal incubator care. When he was one year old, he had two generalized febrile convulsions. He had a history of short stature in his follow-ups. The first sibling who had similar complaints was in a more severe phenotype. He said his first word when he was 5 years old, but still could not make a sentence, started walking at age 2, and now he

can go down and up the stairs. On physical examination, his height was 100 cm (<3 p.), weight 12 kg (<3 p.), and head circumference 44.5 cm (<3 p.). he had moderate intellectual-motor disability, global developmental retardation, short stature, dysmorphic findings (microcephaly, triangular facial structure, strabismus, bilateral ptosis, hypertrophic palate, tooth anomaly (eruptive tooth structure)), pectus excavatum, behavioral problems, hyperactivity, mild stereotypical movements, mild drooling, repetition of words and movements but not neurocutaneous findings (Figure 1). There was no loss of strength. There were hypoplastic corpus callosum and brain stem compartments, and slightly dilated lateral ventricles in cranial MRI (Figure 3). No pathology was detected on echocardiography.

In the chromosome analysis, there was a derivative structure of the long (q) arm of chromosome 7. As a result of the unbalanced transfer of balanced translocation of the father to the child, there was a deletion from the q36 region to the terminal of chromosome 7, and the part of from p15 to the terminal of chromosome 5 was translocated to this region. Accordingly, partial monosomy of chromosome 7 and partial trisomy of chromosome 5 were observed. This result was confirmed with the subtelomeric FISH analysis (46,XY.ish der(7)t(5;7)(p15+;q36)(5pter+;7qter-)pat).

In the microarray analysis, 14.394.065 kb gain (number of markers: 293) covering the 5p15.33-p15.2 region (57 entries in OMIM Gene Map, 23 of which are phenotype related), and 8.702.559 kb loss (number of markers: 263) covering the 7q36.1-q36.3 region (62 entries in OMIM Gene Map, 27 of which are phenotype related) were detected (arr[GRCh37] 5p15.33-p15.2 (50,093-14,444,157)x3, 7q36.1-q36.3 (150,421,573-159,124,131)x1) (Figure 1).

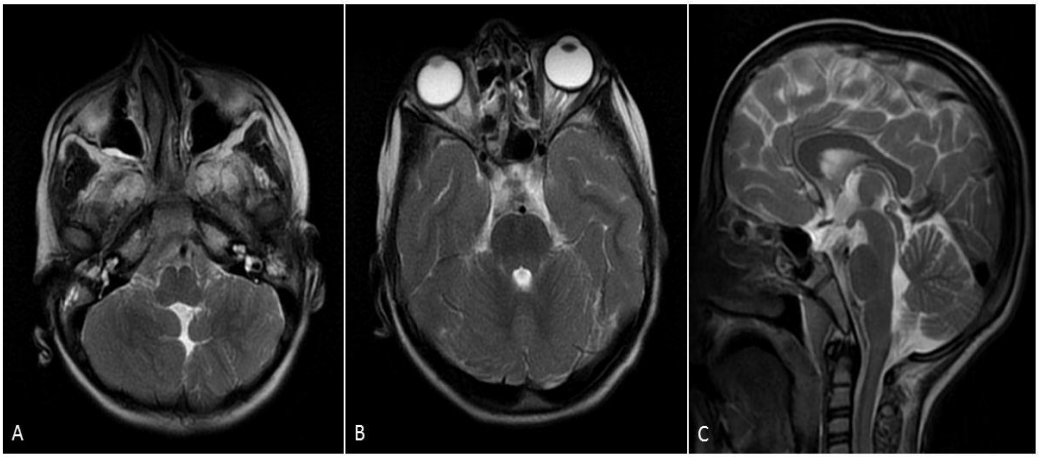

Figure 3. 8-year-old male. A) Mild dysmorphism in cerebellar sulcus at the level of cerebellum inferior on the axial T2-weighted image. B) Slight pachygyria in bilateral temporal gyri on the axial T2-weighted image. C) Sagittal T2-weighted image shows brain stem compartments and corpus callosum in a normal configuration, while mild hypoplasia is seen in the inferior cerebellar vermis.

Discussion

Reciprocal translocation is one of the most common structural anomalies in humans and generally harmless, however, it is associated with an increased risk of a fetus with malformations (9). In general, translocation carriers have a high-risk rate for pregnancy losses. Stern et al. reported that chromosomal translocations were present in 3.2% of couples with recurrent implantation failures (10). Spontaneous abortion risk of couples with balanced reciprocal translocation has been reported to be 50% and the risk of having children with an unbalanced karyotype as 20% (1, 11). In the family mentioned in this article, a father with a balanced translocation carrier and a mother with normal karyotype had no history of pregnancy loss, but two children had two different rare clinical pictures due to unbalanced translocation. Coexistences of 5p partial trisomy with 7q partial monosomy and 5p partial monosomy with 7q partial trisomy in children due to balanced translocation of chromosomes

5 and 7 in the parent have not been reported before, however, cases of t (5: 7), 5p monosomy (Cri du Chat syndrome) or trisomy, and 7q monosomy or trisomy have been reported separately (12-15).

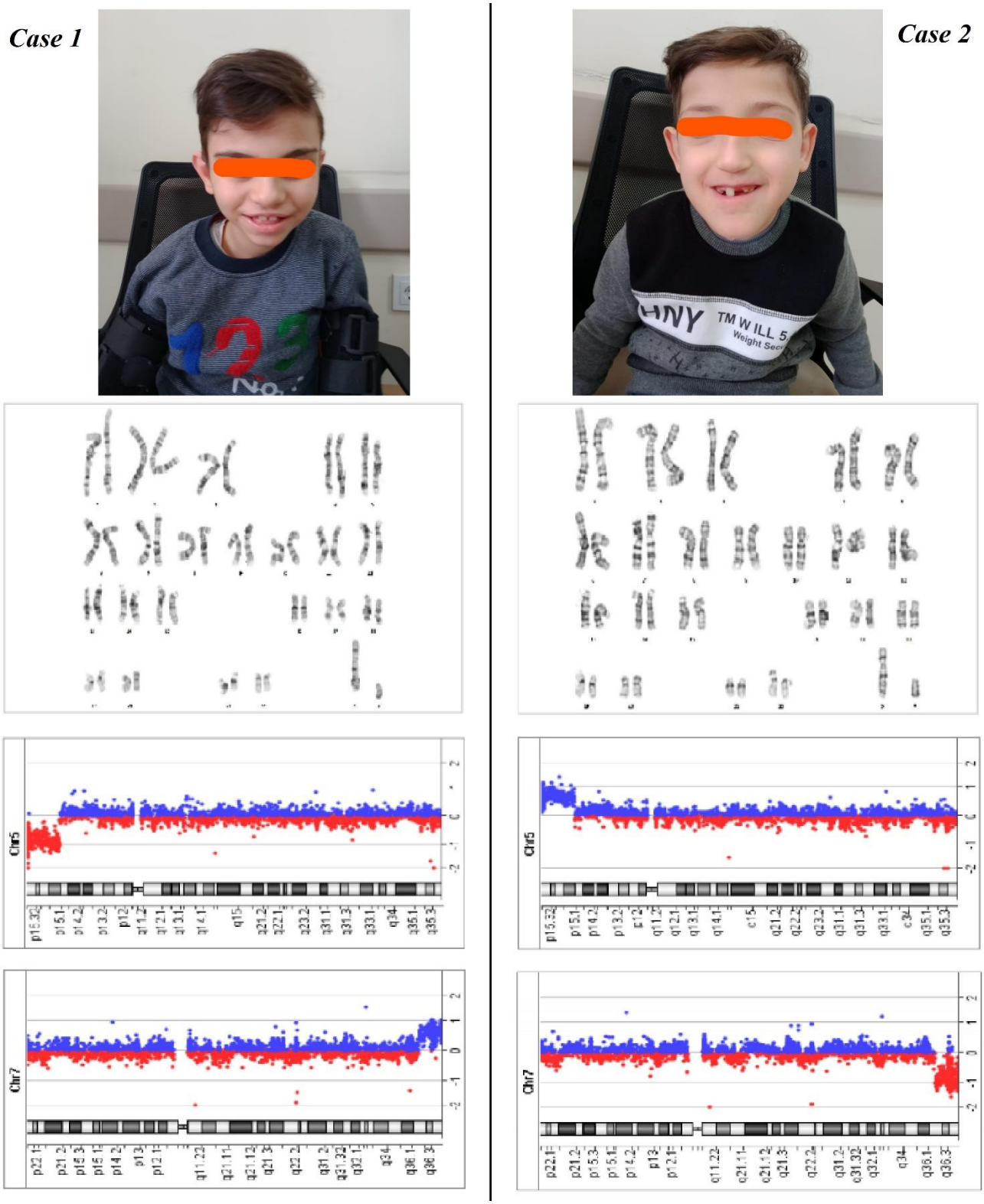

Figure 1. Photographs and images of karyotype and microarray analysis images of patients

In cases of chromosome 7q partial trisomy arising from translocations between chromosome 7 and another chromosome, the phenotype is linked to the chromosomal segment with increased copy number at 7q and the deleted segment of the other chromosome. However, the phenotypic effect of a large 7q duplication is more important than the smaller terminal deletion of the other chromosome (16). The phenotypic features reported

in partial trisomy 7q are not specific and also occur in other chromosomal rearrangements, so this makes phenotype-genotype correlation quite difficult. Some common but nonspecific features are macrocephaly, frontal protrusion, developmental retardation, psychomotor retardation, low ears, short neck, subsequent scoliosis, and genitourinary system abnormalities. It has been reported that a shortened lifespan is associated only with duplication of the entire arm (17).

5p deletion, also known as 5p monosomy, Cat Cry Syndrome or Cri du Chat Syndrome, is a spectrum disorder characterized by microcephaly, round face, hypertelorism, micrognathia, epicanthal folds, low ears, hypotonia, severe psychomotor and intellectual disability, high pitch crying at birth, low birth weight, weak muscle tone and some medical complications (12). The deletion can range in size from very small to large enough to cover the entire short arm. Although most deletions occur *de novo*, approximately 12% are caused by the unbalanced separation of translocations in one of the parents or recombination (18). Our first case had 7q duplication and 5p deletion. In addition to the non-specific features found in both chromosome anomalies such as intellectual disability, hypotonia, and developmental retardation, there were findings of only 7q duplication such as scoliosis and 5p deletion such as microcephaly. However, there were findings such as strabismus, cryptorchidism, hyperpigmented spots, and polydactyly of the foot, which were not reported previously in both chromosome anomalies.

In chromosome 7q deletion syndrome, the severity, signs, and symptoms of the disease depend on the size and location of the deletion, and which genes are involved. Among the features frequently seen in patients with 7q deletion syndrome, there are developmental retardation, hypotonia, short stature, speech and language impairment, speech apraxia, sometimes oral-motor dyspraxia, dysarthria, receptive and expressive language impairment, hearing loss, behavioral problems, and specific facial features. Individuals with great deletions in this region also showed intellectual disability and autism. Most cases are not inherited, but people can pass their deletions to their children (19). Since there are many genes in this region, it varies clinically according to the affected genes and it is difficult to talk about a uniform 7q deletion syndrome (20).

Common features in patients with chromosome 5p duplication include developmental retardation, intellectual disability, behavioral problems, and distinctive facial features. Most cases are not inherited, but people can pass duplication to their children. In general, when there is a chromosome material gain, associated symptoms can include a combination of physical problems, learning disabilities, and/or behavioral disorders. These symptoms largely depend on the location of duplication in the p-arm and the genes affected. Most people with any material loss or gain will have some degree of learning difficulties and developmental retardation because there are many genes in this chromosome that are important for the normal development and function of the brain (21, 22). In general, children with 5p duplication have hypotonia, macrocephaly, craniofacial anomalies, arachnodactyly, and intellectual-motor disability. Some affected people may have heart defects and seizures. The critical region for heart abnormalities and seizures is 5p13.3. Most physical properties are due to the repetition of 5p11 to 5p13.3 bands. The critical region for developmental retardation and intellectual disability is thought to be 5p14-5p15. While the 5p14-5p15 region is normal, it has been reported that there are normal development and mental state in patients with duplication at the terminal (22). Our second case had a moderate intellectual disability, global developmental retardation, dysmorphic facial findings, pectus excavatum, stereotypic movements, and behavioral disorders. The patient had duplication in the 5p15.33-p15.2 region, and as mentioned above, there was no developmental retardation and intellectual disability in anomalies covering areas outside the 5p14-5p15 region. Therefore, we think that global developmental retardation and intellectual disability in our patient are related to 7q deletion.

There are many genes in the affected chromosome regions in both patients, and most of them have been associated with a different phenotype in the OMIM database. Among the genes in the affected area on the chromosome 5p, especially the NSUN2 gene (Gene/Locus MIM number: 610916) and the TRIO gene (Gene/Locus MIM number: 601893) have been associated with intellectual disability (23, 24). The CCT5 gene (Gene/Locus MIM number: 610150) and MARCH6 gene (Gene/Locus MIM number: 613297) may be responsible for the seizures and neurological features in the patient (25, 26). Among the genes in the affected area on chromosome 7q, the KMT2C gene (Gene/Locus MIM number: 606833; Kleefstra syndrome 2, Phenotype MIM number: 617768) has been associated with neuromotor development retardation, many dysmorphic findings, and male genital system defects (27). The DHMN1 gene (Gene/Locus MIM number: 182960) may be responsible for neurological disorders, the SLI4 gene (Gene/Locus MIM number: 612514) for speech disorders, and the AUTS10 gene (Gene/Locus MIM number: 611016) for autistic/stereotypical behaviors (28-30). Mild brain anomalies detected in the cranial MRI may be related to the CDK5 gene (Gene/Locus MIM number: 123831) and SHH gene (Gene/Locus MIM number: 600725) (31, 32). The

LMBR1 (Gene/Locus MIM number: 605522) gene has been previously associated with polydactyly and other digital anomalies (33). Although there are many genes associated with dysmorphism and many more non-specific findings in both chromosome regions, the genes in the 7q region generally appear to be more dominant on the phenotype in both patients. As mentioned before, it has been stated in the literature that changes in the 7q region are more effective (16). In addition, this may be due to the affected part on chromosome 7 being larger than chromosome 5 in our patients.

Study Limitation

For the unbalanced chromosome distributions, meta-analyses with larger sample size will provide better clinical interpretations about the coexistence of these newly defined chromosomal disorders. In addition, the effect of these chromosomal associations would be revealed more clearly with further function test studies.

Conclusion

The coexistences of 5p partial trisomy with 7q partial monosomy and 5p partial monosomy with 7q partial trisomy in children as a result of balanced translocation of chromosomes 5 and 7 in the parent is firstly described in this study. On the other hand, most of the deletion or duplication cases of 7q or 5p defined individually in the literature had milder clinic severity than our cases. This indicates that the more number and size of the affected chromosome regions may refer to the more severe clinical manifestation.

Acknowledgements: *Thanks to Assoc. Prof. Dr. Erkan GOKÇE from Tokat Gaziosmanpaşa University Faculty of Medicine, Department of Radiology due to the help to the radiological evaluation of the patients*

Ethical Approval: none

Author Contributions: *Concept: Ş.Ç Literature Review: Ş.Ç Design: Ş.Ç Writing manuscript: Ş.Ç Critical revision of manuscript: Ş.Ç*

Conflict of Interest: *The author has no conflicts of interest to declare.*

Financial Disclosure: *Authors declared no financial support.*

References

1. Rao L, Kanakavalli M, Padmalatha V, et al. Paternally derived translocation t (8; 18)(q22. 1; q22) pat associated in a patient with developmental delay: Case report and review. Journal of pediatric neurosciences. 2010;5(1):64
2. Zhang S, Zhu J, Qi H, et al. De novo balanced reciprocal translocation mosaic t (1; 3)(q42; q25) detected by prenatal genetic diagnosis: a fetus conceived using preimplantation genetic testing due to at (12; 14)(q22; q13) balanced paternal reciprocal translocation. Molecular Cytogenetics 2021;14(1):1-7.
3. Fan J, Zhang X, Chen Y, et al. Exploration of the interchromosomal effects in preimplantation genetic testing for structural rearrangements based on next-generation sequencing. Mol Genet Genomic Med. 2022;10(9):e2017.
4. Warburton D. De novo balanced chromosome rearrangements and extra marker chromosomes identified at prenatal diagnosis: clinical significance and distribution of breakpoints. American journal of human genetics. 1991;49(5):995.
5. Jacobs PA. Correlation between euploid structural chromosome rearrangements and mental subnormality in humans. Nature. 1974;249(5453):164-5.
6. Paththinige CS, Sirisena ND, Kariyawasam UGIU, et al. A child with multiple congenital anomalies due to partial trisomy 7q22.1 → qter resulting from a maternally inherited balanced translocation: a case report and review of literature. BMC Med Genomics. 2018;11(1):44-.
7. Hall J, Allanson J, Gripp K, Slavotinek A. Handbook of physical measurements: Oxford University Press; 2006.
8. Neyzi O, Saka HN, Kurtoğlu S. Anthropometric studies on the Turkish population-a historical review. Journal of clinical research in pediatric endocrinology. 2013;5(1):1.
9. Nussbaum RL, McInnes RR, Williard HF, et al. Genetics in medicine: Saunders Philadelphia; 2001.
10. Stern C, Pertile M, Norris H, et.al. Chromosome translocations in couples with in-vitro fertilization implantation failure. Human Reproduction. 1999;14(8):2097-101.

11. Cifuentes P, Navarro J, Blanco J, et al. Cytogenetic analysis of sperm chromosomes and sperm nuclei in a male heterozygous for a reciprocal translocation t (5; 7)(q21; q32) by in situ hybridisation. European Journal of Human Genetics. 1999;7(2):231-8.
12. Mainardi PC. Cri du Chat syndrome. Orphanet journal of rare diseases. 2006;1(1):33.
13. Velagaleti GV, Morgan DL, Tonk VS, editors. Trisomy 5p. A case report and review. Annales de genetique; 2000: Elsevier.
14. Scelsa B, Bedeschi FM, Guerneri S, et al. Partial trisomy of 7q: case report and literature review. Journal of child neurology. 2008;23(5):572-9.
15. Inaba T, Honda H, Matsui H. The enigma of monosomy 7. Blood. 2018;131(26):2891-8.
16. Nicolaides KH, Heath V, Cicero S. Increased fetal nuchal translucency at 11–14 weeks. Prenatal Diagnosis: Published in Affiliation With the International Society for Prenatal Diagnosis. 2002;22(4):308-15.
17. Scelsa B, Bedeschi FM, Guerneri S, et al. Partial trisomy of 7q: case report and literature review. Journal of child neurology. 2008;23(5):572-9.
18. Mainardi PC, Perfumo C, Calì A, et al. Clinical and molecular characterisation of 80 patients with 5p deletion: genotype-phenotype correlation. Journal of Medical Genetics. 2001;38(3):151-8.
19. Park IY, Jo YS, Shin JC, et al. De novo 7q deletion with a positive maternal serum triple test screening. Journal of Obstetrics and Gynaecology Research. 2008;34(1):85-7.
20. Ayub S, Gadji M, Krabchi K, et al. Three new cases of terminal deletion of the long arm of chromosome 7 and literature review to correlate genotype and phenotype manifestations. American journal of medical genetics Part A. 2016;170a(4):896-907.
21. Searle B. Chromosomes and Rare Chromosome Disorders in General, Unique The Rare Chromosome Disorder Support Group 1-8. 2016.
22. Dobin S. Chromosome 5, Trisomy 5p NORD: Rare Disease Database; 2019 [Available from: https://rarediseases.org/rare-diseases/chromosome-5-trisomy-5p/.
23. Khan Muzammil A, Rafiq Muhammad A, Noor A, et al. Mutation in NSUN2, which Encodes an RNA Methyltransferase, Causes Autosomal-Recessive Intellectual Disability. The American Journal of Human Genetics. 2012;90(5):856-63.
24. Pengelly RJ, Greville-Heygate S, Schmidt S, et al. Mutations specific to the Rac-GEF domain of TRIO cause intellectual disability and microcephaly. Journal of medical genetics. 2016;53(11):735-42.
25. Copy number variant analysis from exome data in 349 patients with epileptic encephalopathy. Annals of Neurology. 2015;78(2):323-8.
26. Florian RT, Kraft F, Leitão E, et al. Unstable TTTTA/TTTCA expansions in MARCH6 are associated with Familial Adult Myoclonic Epilepsy type 3. Nature communications. 2019;10(1):4919.
27. Koemans TS, Kleefstra T, Chubak MC, et al. Functional convergence of histone methyltransferases EHMT1 and KMT2C involved in intellectual disability and autism spectrum disorder. PLoS genetics. 2017;13(10):e1006864.
28. Gopinath S, Blair IP, Kennerson ML, et al. A novel locus for distal motor neuron degeneration maps to chromosome 7q34-q36. Human genetics. 2007;121(5):559-64.
29. O'Brien EK, Zhang X, Nishimura C, et al. Association of specific language impairment (SLI) to the region of 7q31. Am J Hum Genet. 2003;72(6):1536-43.
30. Alarcón M, Cantor RM, Liu J, et al. Evidence for a language quantitative trait locus on chromosome 7q in multiplex autism families. Am J Hum Genet. 2002;70(1):60-71.
31. Linhares ND, Svartman M, Salgado MI, et al. Dental developmental abnormalities in a patient with subtelomeric 7q36 deletion syndrome may confirm a novel role for the SHH gene. Meta Gene. 2014;2:16-24.
32. Magen D, Ofir A, Berger L, et al. Autosomal recessive lissencephaly with cerebellar hypoplasia is associated with a loss-of-function mutation in CDK5. Human genetics. 2015;134(3):305-14.
33. Semerci CN, Demirkan F, Ozdemir M, et al. Homozygous feature of isolated triphalangeal thumb-preaxial polydactyly linked to 7q36: no phenotypic difference between homozygotes and heterozygotes. Clinical genetics. 2009;76(1):85-90.