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Case Report

3q29 microdeletion syndrome associated with developmental delay and pulmonary stenosis: a case report

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ABSTRACT

Background. 3q29 microdeletion syndrome (OMIM 609425), first described in 2005, is a rare copy number variation (CNV), accompanied by various neurodevelopmental and psychiatric problems. Phenotypic features of the syndrome have not been fully characterized due to the new definition and rarity. Facial dysmorphology, musculoskeletal anomalies, cardiovascular abnormalities, gastrointestinal abnormalities, and dental abnormalities can be seen.

Case. A 28-month-old male patient was brought to the child and adolescent psychiatry clinic with a complaint of speech delay. He had mild dysmorphic symptoms. He was also sensitive to voice and often covered his ears. Balloon valvuloplasty was performed on the postnatal 28th day due to severe pulmonary stenosis. While karyotype was found to be normal, in array-Comparative genomic hybridization (aCGH), copy loss was detected in the long arm of chromosome 3 (arr[hg19] 3q29[196,209,689-197,601,344]x1), which contains approximately 1.4 Mb harboring 30 genes. Genetic counseling was given to the family of the patient who was diagnosed with 3q29 microdeletion syndrome.

Conclusions. In conclusion, we present 3q29 microdeletion syndrome with global developmental delay (GDD), dysmorphic face, hyperacusis, scoliosis, and severe pulmonary stenosis. Performing genetic analysis in patients with developmental delay and congenital heart disease (CHD) for which the cause cannot be explained will prevent these rare diseases from being missed, and the characteristics of the diseases will be better characterized with the reported cases.

Key words: 3q29 microdeletion syndrome, aCGH, developmental delay, child, cardiac defects.

3q29 microdeletion syndrome (OMIM 609425), first described in 2005, is a rare copy number variation (CNV), causing various neurodevelopmental and psychiatric problems.[1] The deletion is usually caused by *de novo* mutations and is rarely inherited.[2] Phenotypic features of the syndrome have not been fully characterized due to its recent definition and rarity. The neuropsychiatric aspects of 3q29 microdeletion syndrome have been emphasized in the literature. Facial dysmorphology, musculoskeletal anomalies, recurrent ear infections, ocular abnormalities, cardiovascular abnormalities, gastrointestinal abnormalities, and dental abnormalities can be detected in 3q29 microdeletion syndrome.

In this article, a 28-month-old male patient who presented with speech delay and was diagnosed with 3q29 microdeletion syndrome is presented, and the importance of genetic evaluation in cases of unexplained global developmental delay (GDD) and congenital heart disease (CHD) is emphasized. This may also contribute to the genotype–phenotype relationship of 3q29 microdeletion syndrome.

Case Report

A 28-month-old male patient was brought to the child and adolescent psychiatry clinic with a complaint of speech delay. The case had

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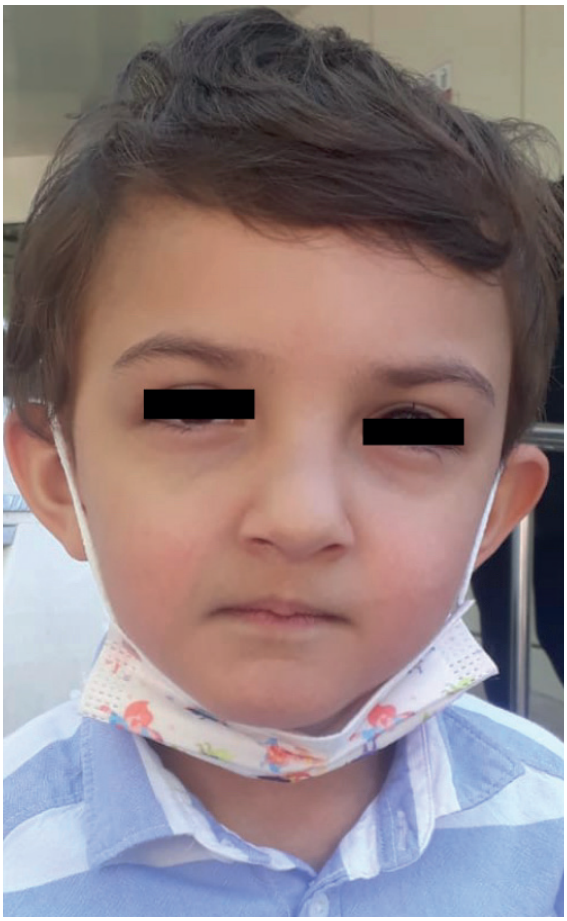
5-6 words and could not make sentences. He was also sensitive to voice, often covering his ears. When he was evaluated in the playroom with his parents, it was observed that he made eye contact, looked when his name was called, performed commands, established joint attention, and played imaginary games. The patient had no seizure history, and his neurological examination was normal.

On physical examination, he had mild dysmorphic symptoms such as posteriorly rotated ears, broad nasal tip, wide forehead, and widely spaced teeth (Fig. 1, 2). There was a *café au lait* spot on his right leg. His height was 100 cm (90th percentile), weight was 15 kg (86th percentile), and head circumference was 49.5 cm (57th percentile).

Since the high trisomy 21 risk was detected in the triple screening test, noninvasive prenatal testing (NIPT) was performed in the prenatal period and the NIPT results showed low trisomy 21 risk. He was born full-term (40th gestational week) with a birth weight of 3,350 kg (50th centile), head circumference of 36 cm (89th centile), and height 50 cm (52nd centile) via cesarean delivery. Balloon valvuloplasty was performed on the postnatal 28th day due to severe pulmonary stenosis. While there was no delay in head and neck control and walking, he spoke his first words at the age of two. He did not have toilet training. There was no abnormality in his newborn hearing screening and visual examination.

The case had a healthy 32-year-old mother and father who were not consanguineous. This case



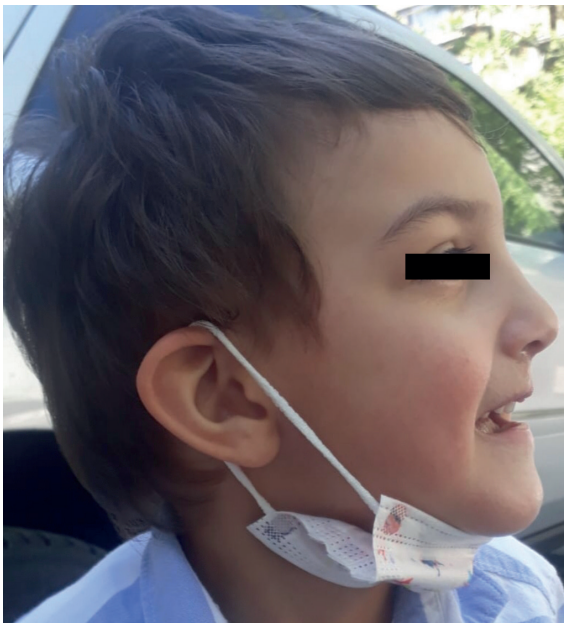


Fig. 1, 2. Patient face and profile at the age of 36 months.

was the first child in the family. A maternal uncle had died on second postnatal day for an unknown reason.

According to the Denver II Development Screening Test, while gross motor skills were comparable to his peers, personal–social (18-19 month), lingual (16-17 month), and fine motor (14-15 month) skills were behind the peers. The Childhood Autism Rating Scale (CARS) score was 21and the Autism Behavior Checklist (ABC) score was 20, both indicating absence of autism. The patient had bilateral Type A tympanograms and presented a normal auditory brainstem response (ABR).

Array-Comparative Genomic Hybridization (aCGH) using the CytoScan® Optima Assay platform and conventional karyotype analysis from peripheral blood were performed on the patient, who was referred to the Medical Genetics department because of his dysmorphic characteristics. Karyotype was found to be normal. In aCGH analysis, copy loss was detected on the long arm of chromosome 3 (arr [hg19] 3q29 [196209689-197601344] x1), which contains approximately 1.4 Mb covering 30 genes (Fig. 3). Genetic counseling was given to the family of the patient on diagnosis of 3q29 microdeletion syndrome. During examination for possible additional problems, mild thoracolumbar scoliosis was detected on direct radiography. He was referred to therapy for his developmental delay and was followed up for possible risks. The aCGH test was recommended to the family before future pregnancies to determine whether the detected anomaly is *de novo* or not, and to determine the risk of repetition of the disease. Written informed consent was obtained from the family.

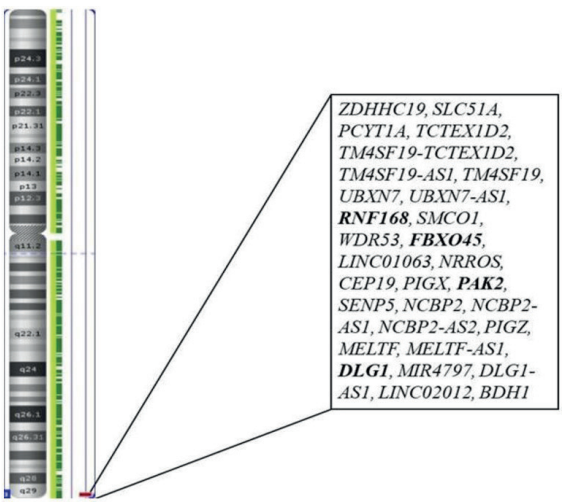


Fig. 3. Copy loss region and affected genes on the long arm of chromosome 3 in presented.

Discussion

Herein a rare case of 3q29 microdeletion syndrome with hyperacusis and pulmonary valve stenosis was presented. The deletion region was as long as 1.4 Mb. The deletion of our patient matched with the typical 3q29 microdeletion syndrome region, but it excluded the *TRFC* gene, which is one of the five disease causing genes in the region.

In addition to high rate neuropsychiatric and neurodevelopmental problems, cardiac malformations like atrial septal defect (ASD), ventricular septal defect (VSD), patent ductus arteriosus (PDA) are seen with 3q29 microdeletion syndrome at a rate of 27%-28%.[3] The cardiac defect is one of the most serious manifestations of this syndrome[4], and it may be the first clinical reflection as in this case. Pulmonary valve stenosis is rarely identified (about 5%) in 3q29 microdeletion syndrome which was also seen in this case.[5] Moreover, hyperacusis has never been reported with this syndrome previously in the literature. The findings in the present case and the frequently reported clinical features are given in Table I.[3,6]

Thirty percent of patients with CHD have genetic defects and they may emerge as various genetic syndromes. For that reason, verification of the existence or absence of genetic defects in newborns with CHD is crucial.[7] By doing this, neurological problems and non-cardiac malformations can be predicted and irreversible damage can be prevented with early intervention.[8] Related to this, research was performed with 200 fetuses with CHD. In that study, whole-exome sequencing (WES)

Table I. Comparison of the clinical features of the patient and reported cases.[4,5]

Phenotypic feature	Previous reported N (%)	Present case
Developmental/Psychiatric		
Speech delay	55/89 (61.8 %)	+
Delayed walking	53/133 (39.8 %)	-
ID*	93/136 (68.3 %)	**
Autism	38/127 (29.9 %)	-
Anxiety	28/96 (75.6 %)	-
Cranio-Facial Dysmorphism		
Broad/High nasal bridge	28/39 (30.7 %)	-
Broad nasal tip	11/28 (39.3 %)	+
Microcephaly	20/38 (52.6 %)	-
Long narrow face	12/36 (33.3 %)	-
Short philtrum	18/36 (50.0 %)	-
Dental abnormalities	36/78 (46.1 %)	+
Musculoskeletal		
Long tapered fingers	12/33 (36.4 %)	-
Scoliosis	6/19 (31.6 %)	+
Clinodactylous toes	9/25 (36.0 %)	-
Chest cavity deformity	12/40 (30.0 %)	-
Others		
Low birth weight (<3rd percentile)	31/80 (38.7 %)	-
Gastrointestinal abnormalities	37/58 (63.8 %)	-
Cardiovascular abnormalities	35/126 (27.8 %)	+
Recurrent ear infections	19/75 (25.3 %)	-
Ocular abnormalities	14/23 (60.9 %)	-
Abnormal skin pigmentation	3/22 (13.6 %)	+

* Intellectual Disability
** IQ test could not be done because of his young age.

was applied to those whose tests were negative. In prenatal chromosome microarray analysis, various chromosomal anomalies including 3q29 microdeletion syndrome were identified in half of the cases.[9] Besides, in a recently published case report, a fetus with VSD was diagnosed with 3q29 deletion prenatally and after genetic counseling, the family decided to terminate the pregnancy.[10]

3q29 microdeletion syndrome provides an important opportunity to investigate genes related to complex neuropsychiatric diseases. 3q29 microdeletion syndrome was first described in six patients with GDD or intellectual disability (ID) ranging from mild to moderate in cases.[1] In later studies, it was reported that the risk of autism increases 34 times in girls and 16 times in boys.[11] Moreover, the 3q29 deletion syndrome, which showed a relationship between cerebellar cortex volumes and psychosis tendency[12], was found to be the highest genetic risk factor (40-fold increased risk) for schizophrenia.[13] Pollak et al.[11] emphasized that these children should be screened starting from an early age, especially with neuropsychiatric and cognitive screening, and followed-up throughout their development.

Despite the strong relationship of 3q29 deletion syndrome with neurodevelopmental disorders, it is unclear how and which genes

affect the phenotype and which cellular mechanisms are impaired. In recent studies, especially *DLG1*, *PAK2*, *FBXO45* genes have come forward with their proven central roles in synaptic communication, and these genes have been associated with ID/GDD, autism, and schizophrenia pathogenesis.[14-17] DLG1 produces a synaptic scaffold protein that interacts with α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) and N-methyl-D-aspartate (NMDA) receptors and takes a role in dendritic spine formation.[18] *PAK2* is from the family of serine/threonine kinases and it is a crucial regulator of cytoskeletal remodeling and dynamics.[19] FBXO45, on the other hand, codes for ubiquitin ligase and regulates glutamate release by mediating Munc13-1 degradation that is a necessary protein for the preparation of presynaptic vesicles.[20] Psychiatric symptoms are considered resulting from synergistic interactions of these gene products rather than individual impacts of genes in deletion area.[21,22] These genes, which have important roles in nervous system development and neurosynaptic maturation are located in the deletion area of this case and this supports the hypothesis in which synaptic dysfunction is involved in GDD/ID pathogenesis. However, despite the similar molecular interactions, the cause behind the fact that autism may arise in 3q29 microdeletion syndromes is still unknown. This may be related to additive variants in the genome or environmental factors.[22]

Furthermore, *RNF168*, which is another gene located in the deletion area is associated with DNA damage repair and is involved in the etiology of immunodeficiency.[23] Its pathological variants cause autosomal recessive RIDDLE syndrome, characterized by immunodeficiency and ID. However, in this case with a heterozygous deletion, no findings suggested immunodeficiency. Likewise, biallelic mutations in TFRC (OMIM 190010) gene is related to autosomal recessively inherited immunodeficiency 46 (OMIM 616740), and this gene is not encompassed in our patient's deletion.[10]

The aCGH method is used as a first-line clinical diagnostic genetic test for further investigation in unexplained GDD/ID cases despite detailed evaluations of history, hearing and vision, and EEG recordings (in suspicious cases). Furthermore, in cases where cardiac defects are seen in addition to dysmorphic symptoms, neuropsychiatric or neurodevelopmental problems, gastrointestinal or musculoskeletal abnormalities, it is important to test for CNVs.[24] Besides, through aCGH, it has become easier to identify many new microdeletion/microduplication syndromes in individuals with idiopathic ID/GDD or congenital anomalies. For the same microdeletion/microduplication syndrome, the size of the associated region and accordingly gene contents differ in cases. To establish phenotype-genotype relationships much clearly, detailed molecular analysis should be performed on more patients.

In conclusion, the determination of a CNV in this patient, urged us to consider other possible risks and follow the patient closer. These findings suggest to clinicians that children diagnosed with 3q29 microdeletion syndrome should be evaluated with cardiac and developmental scans. Furthermore, routine psychiatric follow-ups are recommended for these children due to developmental delays or other possible psychiatric problems.

Ethical approval

Written informed consent was obtained from the family.

Author contribution

The authors confirm contribution to the paper as follows: study conception and design: DK; data collection: DK, ZYÇ; analysis and interpretation of results: DK, ZYÇ; draft manuscript preparation: DK, ZYÇ. All authors reviewed the results and approved the final version of the manuscript.

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Conflict of interest

The authors declare that there is no conflict of interest.

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