Hale Onder Yılmaz et al, 2020;3(2):104–107.
https://doi.org/10.24911/JBCGenetics/183-1592502000

CASE REPORT

A case of de novo microdeletion with combination of 1q21.1 and 14q32.2q32.31

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ABSTRACT

Background: Chromosomal microarray is considered as the first-line diagnostic genetic test in all individuals with intellectual disability (ID) and attention-deficit disorders. In recent years, the use of chromosomal microarrays routinely for this purpose has resulted in the identification of many new microdeletion and microduplication regions connected with these clinical situations, including the 1q21.1 and 14q32.2q32.31 microdeletions.

Case Presentation: A 5-year-old male patient came to the clinic because of ID, hyperactivity, growth retardation, and speaking difficulty. We determined strabismus on both the eyes, and he was myopic. He had a high palate, little, and sparse teeth. On the right hand, there was a simian line. Both undescended testes were brought down with surgery. In addition, he had got an inward penis head. He had joint laxity in most of the joints. He had pes planus and talipes valgus. Therefore, we decided to make array-comparative genomic hybridization analysis and the result came 1368.001 kb deletion on 1q21.1 between chr1: 146023922 and 147391923 nucleotides and 992.003 kb deletion on 14q32.2q32.31 between chr14: 100453009 and 101445012 nucleotides according to "Human Genome Build 37" (The result was confirmed by a fluorescent *in situ* hybridization method performed to determine the particular deleted regions).

Conclusion: Here, we report the first case presented with ID, hyperactivity, growth retardation, and speaking difficulty with other findings and has a combination of *de novo* 1q21.1 and 14q32.2q32.31 microdeletions. Although several research groups have reported similar results with similar regions separately, this study is the first of its kind revealing the effects of this combination to clinical outcome.

Keywords: 1q21.1 microdeletion, 14q32.2q32.31 microdeletion, growth retardation.

Introduction

In many genetic diseases, neurocognitive impairment accompanies several additional findings at the same time, in the same patient. These genetic disorders are named as genetic syndromes. There are two common explanations for the mechanism of genetic syndromes. One of them is pleiotropy, in which a mutation in a single gene results in multiple effects on separate organ systems. Another explanation is contiguous gene syndromes, in which the patient can have deletions (missing genetic material) or duplications (extra genetic material) involving a certain region of a chromosome containing different genes (1). Different methods can determine these two different phenomena. Transcriptomic analysis methods can determine the former phenomenon, and the latter one can be detected by chromosome analysis, array-comparative genomic hybridization (CGH), and fluorescent *in situ* hybridization (FISH) analysis depending on the size of region deleted or duplicated.

Chromosomal microarray is now considered as the first-line diagnostic genetic test in all individuals with intellectual disability (ID) and attention-deficit disorders (2). In recent years, using chromosomal microarrays routinely for this purpose, has resulted in the identification of many new microdeletion and microduplication regions connected with these clinical situations, including 1q21.1 and 14q32.2q32.31 microdeletions. Isolate 1q21.1 region microdeletions are mainly associated with congenital heart diseases, ID, and several dysmorphic features. 1q21.1 region is a common cause of syndromic ID, but only several patients with ID who have a terminal 14q32 deletion have been reported. Patients with an interstitial microdeletion in the 14q32 region seem to be rarer (only three patients have been reported to date) (3-5).

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Received: 20 June 2020 | **Accepted:** 07 September 2020

Here, we report the first case which has both 1q21.1 and 14q32.2q32.31 interstitial microdeletions identified by array-CGH methods.

Case Report

A 5-year-old male patient came to the clinic because of ID, hyperactivity, growth retardation, and speaking difficulty (Figure 1, permission was given only for this photo by family). His mother and father were not relative, and the family history was unremarkable (he is the index case in the family). At birth, his mother was 24, and the father was 36 years old. He was born with the cesarean section as 2.5 kg. During the intrauterine period, he took intrauterine growth restriction diagnosis, but the history of pregnancy was unremarkable. On physical examination (when the patient was 60 months old), he was 103 cm height (3th-10th percentile) and 17 kg (25th percentile) weight. His head circumference was 51 cm (50th percentile). We determined strabismus on both the eyes, and he was myopic. He had a high palate, little, and sparse teeth. On the right hand, there was a simian line. Both the undescended testes were brought down with surgery. In addition, he had got an inward penis head. Most of the joints have joint laxity. He had pes planus and talipes valgus. His laboratory findings and metabolic scanning were not meaningful. Abdomen ultrasonography, ECHO, and hearing test were normal. The brain magnetic resonance imaging was reported as cerebral white matter hypomyelination, dysgenesis of corpus callosum, and enlargement of the extra-axial distance. We performed a chromosome analysis from peripheral blood, and the result was 46, XY. Hence, we decided to make array-CGH analysis, and the result came 1368.001 kb deletion on 1q21.1 between chr1: 146023922 and 147391923 nucleotides and 992.003 kb deletion on 14q32.2q32.31 between chr14: 100453009 and 101445012 nucleotides according to "Human Genome Build 37" (The result was confirmed by the FISH method to determine the particular deleted regions). After this result, we desired to know whether these findings were coming from parents, and we performed array-CGH to parents. Still, their results were normal (the same FISH probes were performed to the parents to know the particular regions deleted in the patient, and the results were normal). We also performed chromosome analysis from peripheral blood to parents to determine whether they had a chromosomal translocation that can cause this imbalance in the patient. However, the results were also normal.

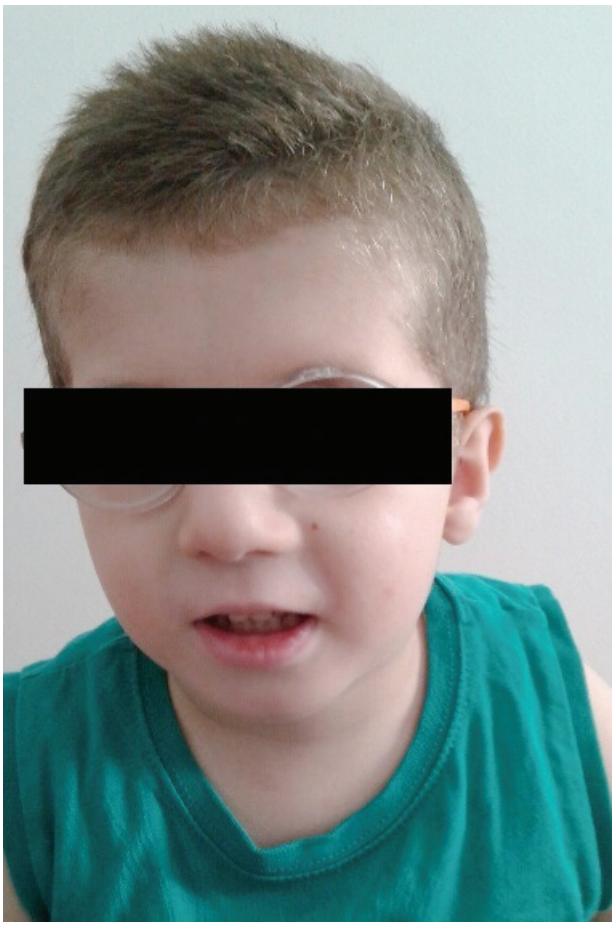

Figure 1. *The case.*

Discussion

Here, we report the first case who had the combination of 1q21.1 and 14q32.2q32.31 microdeletions. Although these findings were accepted as a variant of uncertain significance in https://decipher.sanger.ac.uk/search database, it was accepted as pathogenic in https://research.nhgri.nih.gov/CGD/search database. We cannot compare the patients with previous similar case because of the lack of data in the literature, but we compare clinical findings with isolate 1q21.1 or 14q32.2q32.31 microdeletions separately (Tables 2 and 3).

Although there is limited knowledge about the effects of both regions on the clinic, there are several similarities between the cases with isolate 14q32.2q32.31 region deletion and the present case. There are two differences that are lack of hypotonia and feeding problems apart from dysmorphic features. The size of the deletion region is the smallest among the previous cases (according to PubMed), and the deletion region is also between 100.400 and 101.500 base pairs (3). This smaller loss may cause a less clinical outcome. Unfortunately, we do not know whether the effects of this deletion combination are positive or negative to clinical outcome. Regarding 1q21.1 deletion, almost all clinical findings are matched with the present case. The remaining five negative findings are only seen in 25% of all cases, indeed (6).

Overall, this case presents almost all findings in terms of both the deletion regions. In addition, there are several orthopedic findings which have not been mentioned in the previous publications yet. They are pes planus, taliper valgus, and generalize joint laxity. Furthermore, simian line and little and sparse teeth have also been not mentioned before.

Table 1. *Deleted regions and genes (with OMIM number) involved in these regions in our case.*

Location	Size	Genes involved in this region
1q21.1	1368.001 kbp	NBPF10 (614000), HYDIN2 (610813), NBPF12 (608607), PRKAB2 (602741), FMO5 (603957), CHD1L (613039), BCL9 (602597), ACP6 (611471), GJA5 (121013), GJA8 (600897)
14q32.2q32.31	992.003 kbp	DEGS2 (610862), YY1 (600013), SLC25A47 (609911), SLC25A29 (615064), WARS (191050), DLK1 (176290), MEG3 (605636), RTL1 (611896), MIR431 (611708), MIR433 (611711), MIR127 (611709), MIR136 (611710), MEG8 (613648), SNORD113-1 (613650), SNORD114-1 (613651)

Table 2. *Comparison between isolate 14q32.2q32.31 interstitial deletion cases and present cases.*

	Buiting et al. (4)	**Béna et al.** (3)	**Zada et al.** (5)	**Present case**
Deletion position in 14q32.2	100.396-101.502	100.400-101.500	100.388-101.506	100.453-101.445
Sex	Female	Female	Female	Male
Age (years)	14.5	4	20	5
Pre- and postnatal growth retardation	+	+	+	+
Hypotonia	+	+	+	−
Feeding problems	+	+	+	−
Precocious puberty	+	?	+	?
ID	+	+	+	+
Dysmorphism	−	High forehead, small chin, posteriorly rotated ears, and flat feet	Flat face, flat philtrum, thin lips, tapering fingers, clinodactyly of the fifth finger on the right hand, and clubbing feet toes	High palate, little and sparse teeth, simian line on right hand, undescended testes, inward penis head, pes planus and talipes valgus, and joint laxity
Others	−	Hypermetropia	−	Myopia, strabismus

+: present; −: not present; ?: undetermined yet.

Table 3. *Comparison of clinical findings between 1q21.1 deletion syndromes and our case.*

1q21.1 deletion syndromes (6-8)	**Present case**
Developmental delays (50%-75%)	+
Mild-to-moderate ID (25%-50%)	+
Mild dysmorphic facial features (frontal bossing, deep-set eyes, and bulbous nose) (>75%)	Deep-set eyes and bulbous nose
Microcephaly (25%-50%)	−
Short stature (25%-50%)	+
Attention-deficit/hyperactivity disorder (10%-25%)	+
Cardiac abnormalities (10%-25%)	−
Hypotonia (10%-25%)	−
Seizures (10%-25%)	−
Autism/autistic features (<10%)	+
Brain malformations (<10%)	+
Genitourinary abnormalities (<10%)	+
Sensorineural deafness (<10%)	−

+: present; −: not present

Conclusion

We detected a rare case with 1q21.1 and 14q32.2q32.31 microdeletions by using array-CGH analysis. This type of combination has not been previously reported. This case report demonstrates the value of applying array-CGH testing for accurate genetic diagnosis that can help to improve the patient care and provide proper counseling for the family. In addition, both deletion regions contained different genes (Table 1), and furthermore, the studies may be performed based on these findings in the future. These further studies could be targeted for *HYDIN* gene and *YY1 gene* which are expressed in brain and connected with microcephaly (7) and among different parts of the body associated with Gabriele de Vries Syndrome (OMIM:617557), respectively.

Funding
None.

Declaration of conflicting interests
The authors of this article have no affiliations with or involvement in any organization or entity with any financial interest or non-financial interest in the subject matter or materials discussed in this manuscript.

Ethical approval
Ethical approval is not required at our institution to publish an anonymous case report.

Consent for publication
An informed consent was obtained from the parents.

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