The Turkish Journal of Pediatrics 2018; 60: 94-98
DOI: 10.24953/turkjped.2018.01.015

Case Report

Clinical findings in cases with 9q deletion encompassing the 9q21.11q21.32 region

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Received: 17th February 2017, Revised: 27th April 2017, Accepted: 10th June 2017

SUMMARY: Tuğ E, Ergün MA, Perçin EF. Clinical findings in cases with 9q deletion encompassing the 9q21.11q21.32 region. Turk J Pediatr 2018; 60: 94-98.

We report on a case with developmental delay and dysmorphic craniofacial features, and a novel~15.2 Mb interstitial deletion within 9q21.11q21.32 confirmed with array comparative genomic hybridization (aCGH). A twenty-two month old boy with inability to walk without support, absent speech, and attention deficit and hyperactivity disorder was seen in our clinic. His craniofacial examination revealed relative macrocephaly, facial asymmetry, frontal bossing, sparse medial eyebrows, hypertelorism, broad base to nose, smooth philtrum, large mouth, operated cleft lip and wide spaced teeth. The high resolution binding (HRB) chromosome analysis revealed an interstitial deletion 46,XY,del(9)(q21) confirmed by aCGH revealing; 46,XY,der(9)(pter→q21.11::q21.32→qter).arr9q21.11q21.32(71,069,763-86,333,272)X1dn. Genotype-phenotype correlations of sixteen cases with 9q21 deletion having different breakpoints and variable length revealed common characteristic features including severe developmental delay, epilepsy, neuro-behavioural disorders and facial dysmorphism including hypertelorism, smooth philtrum and thin upper lip. The smallest overlapping deleted region in all defined cases to date including our case comprised four genes. Among these deleted genes as in our case, especially *RORB* is considered to be a strong candidate for neurological phenotype.

Key words: 9q21 microdeletion, intellectual disability, developmental delay, speech disorder, autism, behavioral problems.

Cytogenetically visible interstitial deletions of 9q do not define a characteristic phenotype, due to the presence of very few cases[1]. Lately, nine cases with a novel microdeletion at 9q21.13 presenting with mental retardation, speech delay, epilepsy, and characteristic facial features have been reported by Boundry-Lapis et al.[2]. In addition to these, one case with epilepsy, eyelid myoclonia and generalized tonic-clonic seizures and autism has been reported by Bartnik et al.[3] and another case with mild intellectual disability and idiopathic partial epilepsy has also been reported by Baglietto et al.[4]. The deleted segments in all cases with interstitial deletions of chromosome 9q21.11-21.32 spanned from 2.2 to 12.6 Mb and included a variable number of genes.[2] In addition to these eleven cases, four cases with deletions localized to the same region with similar clinical phenotypes have been reported in the DECIPHER database. The smallest overlapping deleted region extending 750 Kb included four genes in all reported cases.[2,3] The array comparative genomic hybridization (aCGH) is very useful to identify involved genes in gains or losses of genetic material and enables to delinate genotype-phenotype correlations.[2] Here, we present a rare and the youngest case yet reported of *de novo* interstitial deletion of chromosome 9q21,with the genotype-phenotype correlations and the review of the literature.

Case Report

A twenty-two-month-old boy was admitted to our clinic for intellectual and developmental

Presented at Gevher Nesibe Medical Days 2016 and Medical Genetics and Clinical Practices Congress. Erciyes Medical Journal 2016; 38 (3):14. Oral Presentation.

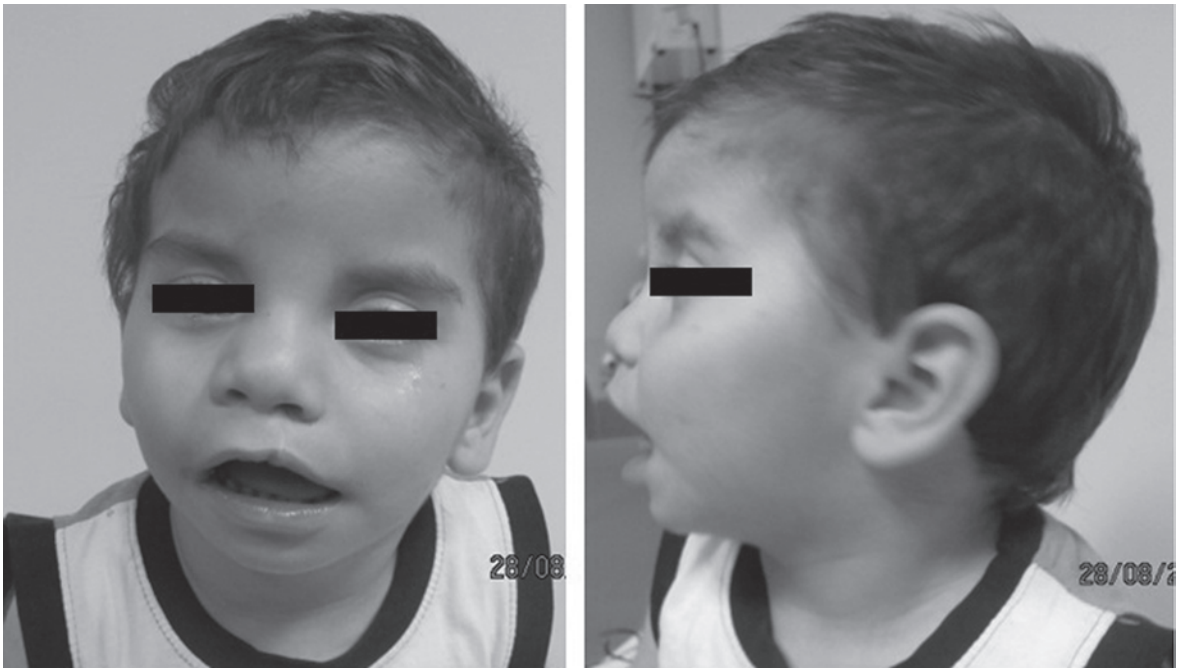

Fig. 1. The craniofacial appearance of the case (a. full face and b. profile): Relative macrocephaly, facial asymmetry, frontal bossing, sparse medial eyebrows, hypertelorism, broad base to nose, smooth philtrum, large and open mouth, thin upper lip, operation scar on the lip and posterior rotated ears.

disability and absent speech. He was born with a cleft lip at term to healthy non-consanguineous parents after an unremarkable gestation via cesarean. His birth weight was 3,400 g (25-50th centile), length was 50 cm (50th centile), and head circumference unknown. He was hospitalized 15 days after birth due to respiratory distress and excessive vomiting. He had surgery due to his cleft lip at 3 months. Early motor-milestones were delayed; inability to walk without support and absent speech at 22 months. He had behavioral disorders such as aggressive and poor communication. In the physical examination, his weight, height and head circumference were 10,500 g (3-10th centile), 85 cm (10-25th centile) and 49 cm (50th centile), respectively. He had craniofacial dysmorphic features including relative macrocephaly, facial asymmetry, midface flattening, frontal bossing, sparse medial eyebrows, hypertelorism, broad base to nose, smooth philtrum, large and open mouth, thin upper lip, operation scar on the lip, wide spaced teeth and posterior rotated ears (Fig. 1). Brain magnetic resonance imaging (MRI) showed an incision in the upper segment of corpus callosum determined as a variation.

The Denver Developmental Screening test that had been performed at 1 year and 11 months of age revealed common developmental disorder, and the personal and social development with thin-motion development; language development and coarse movement development was found to be compatible with 10, 9 and 14 months, respectively. When he was re-examined at the age of 5 years, he had attention deficit and hyperactivity disorder (ADHD) and had seizures since 1 year. Electroencephalogram (EEG) showed focal epileptic disorder. Echocardiography and renal ultrasonography (USG) were normal.

High resolution cytogenetic analysis was

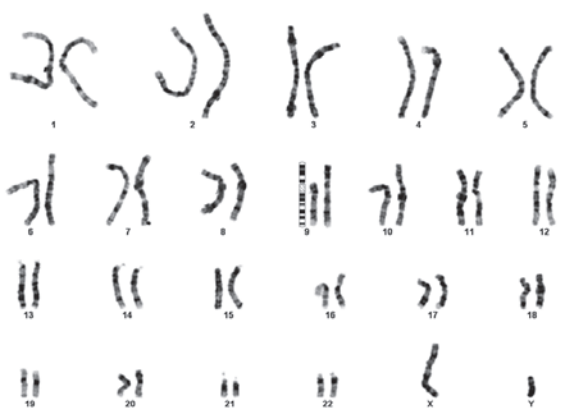

Fig. 2. GTG banded karyotype of the proband and ideogram corresponding to 550 band levels as described by ISCN.

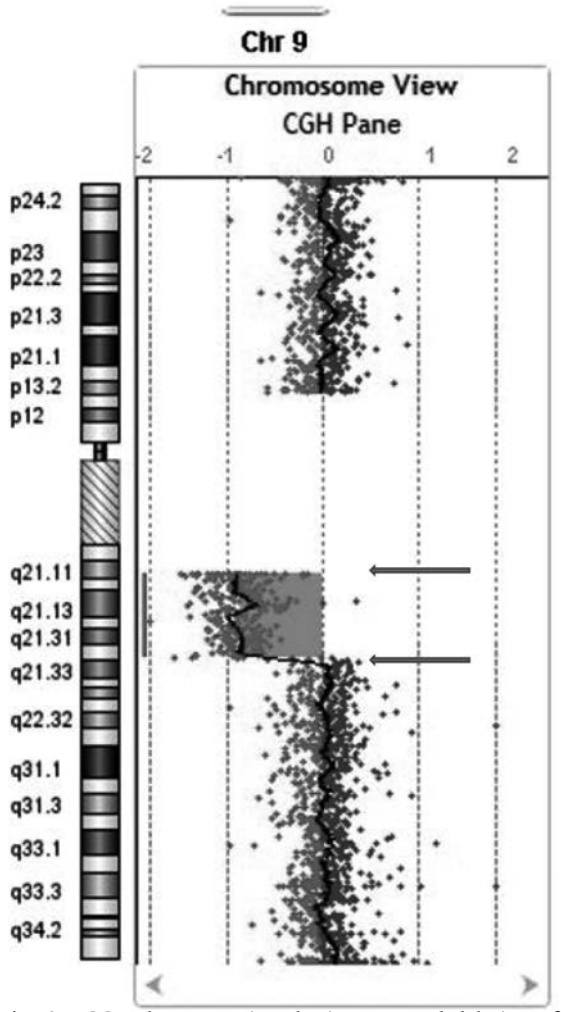

Fig. 3. aCGH demonstrating the interspersed deletion of ~15.2 Mb at 9q21.11-q21.32; arrows indicate the deleted region on chromosome 9q21.

performed on cultured lymphocytes by G-banding according to standard procedures. We identified a *de novo* interstitial deletion in 9q21 locus (Fig. 2). For identified affected genes in the deleted region, we performed molecular karyotyping using the SurePrint G3 Human GE 8x60K Microarrays (Agilent Technologies, Santa Clara, CA, USA) according to the manufacturer's protocol. Molecular karyotype was 46,XY,der(9)(pter→q21.11::q21.32→qter). arr 9q21.11q21.32(71,069,763-86,333,272) X1dn.The deleted region spans ~15.2 Mb at 9q21.11 q21.32 (Fig. 3).

Written informed consent was obtained from the patients' guardians.

Discussion

We evaluated the findings of our case with the sixteen cases with interstitial deletion on 9q21.[2,3,4] Four cases of these with deletions localized on the same chromosomal region with similar clinical phenotypes have also been reported in the DECIPHER database. All cases previously presented and our case's karyotypes and sizes of deletion on 9q21 locus, age at diagnosis and clinical findings are shown in Table I. Although there have been limited cases reported with 9q21 deletions, our molecular karyotyping results enabled us to perform a genotype-phenotype correlation with the reported genes. Especially intellectual disability (93.75%), developmental retardation (87.5%), speech disorder (68.75%), seizure (81.25%), autistic behaviour (56.25%)/ behavioural problems (46.6%) and facial dysmorphism (100%) were cardinal findings of 9q21 microdeletion syndrome. Hypertelorism, smooth philtrum, large and open mouth and thin lips were common dysmorphic features in these cases (Table I). Clinical findings of the case including cleft lip, midface flattening, large mouth, broad base of nose suggest that 9q21 deletion leads to a craniofacial phenotype. The nonspecific midline MRI findings are supportive of these conditions. Also, we want to emphasize that our case is the youngest case yet reported.

The brain MRI findings differ between the cases. Chiari type I malformation, hippocampal asymmetry, hypoplasia of corpus callosum, delayed myelinisation and arachnoid cyst are reported in cases described by Boudry-Labis et al.[2]. The MRI of our case revealed an incision in the upper segment of the corpus callosum. Also, in all of the cases including our case, behavioral problems, hyperactivity or autism were remarkable.[2,3]

Regarding the deleted genes, our case was similar with Boundry-Labis et al.[2]study. They proposed the smallest deleted region in all cases with overlap extending 750 Kb which included four genes *RORB, TRPM6, NMRK1, OSTF1,* and also suggested that these four genes seem to be candidate genes for the neurological phenotype.[2] However, Baglietto et al.[4] claimed that *NMRK1* and *OSTF1* are not expressed in the brain and do not seem to be relevant candidates for neurodevelopmental disorders. *TRPM6* has been associated with a known human disorder (OMIM 602014). Homozygous

Table I. Previously Presented Patients and Our Patient's Karyotypes and Sizes of Deletion on 9q21 Locus, Age at Diagnosis, Clinical and Radiological Findings.

	Boudry-Labis et al.[2]									Bartnick et al.[3]	Baglietto et al.[4]	Decipher				Our Case	Total (%)
Patients	1	2	3	4	5	6	7	8	9			1	2	3	4		
Karyotype	46,XY	46,XY,t(2;9)(q32;q13)dn	46,XY,t(1;16)(p13.3;q21) mat	46,XY	46,XY	46,XX	46,XY	46,XX	ND	46,XY	46,XX	46,XY	46,XY	UK	UK	46,XY,del(9)(q21q21)dn	Normal 10/16 (62.5)
Locus*	9q21.13	9q21.13	9q21.13q21.33	9q21.2	9q21.13	9q21	9q21	9q21	9q21	9q21.13	9q21.13	9q21	9q21	9q21	9q21	9q21.11q21.32	9q21.13
Deletion Size (Mb)	5.6-5.9	6.5-6.7	7.1-7.3	9.9	2.2	11.0	2.2-2.3	6.8	12.6	2.57	1.04	6.4	10.36	11.13	7.9	15.2	1.04-15.2
Age at diagnosis (years)	8	8	15	2	12	6	16	15	4.5	2	12	-	-	-	-	1 age 10 month	1-16
Clinical and radiological findings																	
Intellectual Disability	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	15/16 (93.75)
Developmental Retardation	+	+	+	+	+	+	+	+	+	-	-	+	+	+	+	+	14/16 (87.5)
Hypotonia	-	-	-	-	-	-	+	+	+	-	-	+	UK	UK	UK	-	4/13 (30.7)
Speech disorder/ speech delay	+	+	+	+	-	+	+	+	+	-	-	+	+	-	-	+	11/16 (68.75)
Epilepsy/ Seizure	+	-	+	-	+	+	+	+	+	+	+	+	+	+	-	+	13/16 (81.25)
Autistic behaviour	+	+	+	+	+	+	-	+	-	+	-	+	-	-	-	-	9/16 (56.25)
Behavioural problems/ Hyperactivity	UK	-	+	+	+	+	-	-	-	-	-	-	+	+	-	+	7/15 (46.6)
Ocular abnormalities	-	Strab.	-	-	-	Strab. Hypero.	-	-	Astigm.	-	Strab.	-	-	-	Strab.	-	5/16 (31.25)
Skeletal malformations	-	-	-	Short hands	-	-	-	Short/ broad hands, tapering fingers, thoraco-lumbar scoliosis, spinal fusion	Bilateral clinodactyly of the 5th fingers	-	-		-	-	Proportionate short stature	-	4/16 (25)
Hyper-trichosis	+	+	-	+	-	-	-	-	-	-	-	Broad foot -	-	-	-	-	3/16 (18.75)
Brain MRI	Chiari type I		Normal	Normal	Slight hippocampal asymm.	Corpus callosum hypop.	Normal	Normal	Delayed myelinisation, arachnoid cyst	-	-		-	-	-	An incision in the upper segment of corpus callosum	5/16 (31.25)
Dysmorphic features										NA			NA	NA	NA		**
Low hairline		+						+			+	+					3/12 (25)
Hyper-telorism	+							+	+		+					+	5/12 (41.6)
Upslanting palp. fiss.		+	+								+						3/12 (25)
Long philtrum		+		+	+	+					+						5/12 (41.6)
Open mouth						+						+				+	3/12 (25)
Large mouth	+	+														+	3/12 (25)
Thin upper lip	+		+	+	+				+		+					+	7/12 (58.3)
High palate						+		+				+					3/12 (25)
Others	Wide nares, Short columella	Midface flattening, Narrow forehead, Synophrys, Smooth philtrum, Slightly massive chin	Bilateral epicanthi	Short nose		Thin hair, Small ears	Large ears	Widow's peak, Long face, Arched eyebrows, Synophrys Downslanting palp. fiss., Prominent chin	Downslanting palp. fiss., Flat nasal bridge, Short nose Micrognathia, Wide-spaced nipples, Shawled scrotum, Sacral dimple			Long face, Narrow forehead, Supernumerary nipples, Shawled scrotum, Joint laxity				Relative macrocephaly Facial asymmetry, Midface flattening, Frontal bossing, Sparse medial eyebrows, Broad base to nose, Cleft lip, Smooth philtrum, Wide spaced teeth, Posterior rotated ears	

ND: Not done; UK: Unknown.*: Common deleted region in all presented cases. Asymm.: Asymmetria; Astigm.: Astigmatism; Strab.: Strabismus; Hypero.: Hyperopia; Hypop.: Hypoplasia; Palp. fiss.: Palpebral fissures. **Note: The patients 2-4 from Decipher database and the case of Bartnick et al.[3] were excluded from this table as the detailed dysmorphic findings of them were not accessible.

or compound heterozygous mutations in this gene are associated with hypomagnesemia with secondary hypocalcemia.[5,6] While calcium measurement in our case was 9.55 mg/dl (normal range 9-11 mg/dl), unfortunately magnesium measurement and *TRPM6* gene sequencing to exclude a mutation of the remaining allele have not been performed. Additionally, our case did not have the clinical findings of generalized convulsions, muscle spasms or tetany which were the manifestations of the hypomagnesemia.

Boundry-Labis et al.[2] proposed *RORB* as a strong candidate for a neurological phenotype such as mental retardation and epilepsy. *RORB* gene was cloned from a rat brain library and its transcripts were found to be expressed only in the brain regarding other tissues.[7,8] Also, *RORB* was demonstrated to be expressed in the temporal cortex of cases with temporal lobe epilepsy.[9] The focal epileptic disorder beginning later in patients may also be associated with *RORB* gene dosage deficiency.

Previous studies indicate that *RORB* regulates neuronal patterning during cortical development[10] and *Rorb*-null rats show disruption in some neurological reflexes and exhibit behavioural changes.[11] Recent studies demonstrated correlation between *RORB* and bipolar disorders.[12,13] The behavioral problems, in our case also supporting these findings whereas, the hyperactivity or autistic behaviour may be related to the lack of compensation for this gene dosage.

As a conclusion, we report on a case having a novel ~15.2 Mb interstitial deletion within 9q21.11q21.32 confirmed with aCGH. As well as intellectual disability, developmental delay, speech disorder, epilepsy, autistic behaviour/ behavioral problems and dysmorphic features including especially hypertelorism, long and smooth philtrum, open and large mouth, thin upper lips are important findings of this deletion. *RORB, TRPM6, NMRK1, OSTF1* genes which are localized in 750 Kb smallest deleted region seem to be candidate genes for the neurological phenotype. Especially *RORB* may be responsible for epilepsy, behavioural problems, hyperactivity or autistic behavior.

Acknowledgements

The authors would like to express their gratitude to the case's parents for their cooperation in the clinical evaluation, analysis and consent for photo release.

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