CASE STUDY

A broad spectrum manifestation in a case affected by 3q29 microdeletion syndrome: a literature review and in silico analysis

Seyed Mokhtar Esmaeilnejad-Ganji, Alireza Paniri, Monireh Golpour, Reza Tabaripour and Haleh Akhavan-Niaki

ABSTRACT

Background and Objective: 3q29 microdeletion syndrome, is a rare condition with a wide spectrum of clinical manifestations from behavioural features including autism to developmental delay such as speech and walking delays caused by a small deletion at 3q29. Low copy repeats surrounding this region prone it to non-allelic homologous recombination. We investigated the karyotype of a 24 years-old patient suffering from skeletal deformity, cardiac anomaly, intellectual disability, and dysmorphic face.

Results: Obtained results from high-resolution banding for 3q29 deletion in a patient revealed subtelomeric deletions in chromosome 3. Furthermore, the analysis of her parents revealed a normal karyotype although her mother showed mild intellectual disability.

Conclusion: We identified a *de novo* 3q29 microdeletion in a non-caucasian subject with several variable phenotypes comprising intellectual disability, skeletal deformities, asymmetric long narrow face with a long thin lip, genitourinary defect, and heart defect.

Keywords: 3q29 microdeletion, cardiac defect, developmental disabilities, skeletal deformity, in silico.

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INTRODUCTION

Chromosomal aberrations constitute the majority of genetic abnormalities and cytogenetic analysis is a powerful tool for investigating the structure and properties of chromosomes. Some of the rare syndromes including 3q29 microdeletion have challenged the decision of genetic counsellors and health care professionals due to their very variable clinical manifestations (1). 3q29 microdeletion syndrome is caused by about 1.6 Mb deletion of 3q29 with an incidence of 1:40000 birth in the population (2). The clinical phenotypes associated with 3q29 deletion syndrome are remarkably variable including some developmental milestone delay, gait abnormality, musculoskeletal abnormalities, urinary voiding dysfunction, heart defects, gastro-esophagal reflux disorder, feeding problems, chronic constipation, anxiety disorder, autism, depression, schizophrenia, facial dysmorphology, chest-wall deformity, and long and tapering fingers (3-5). In this report, we describe a case with 3q29 heterozygous *de novo* deletion by using G-banding and karyotyping analysis as a simple and effective tool.

CASE PRESENTATION

The proband, a 24-year-old female, was born at 39 weeks of gestation with a natural delivery and weighed 3.7kg from healthy non-consanguineous parents. She showed a delay in walking and speech, that began at 2 years old. Her auditory skills were well developed, and she followed sounds around normally. A heart defect was operated on at 2 years old. Skeletal deformities were seen in the first few years after birth and she exhibited passive dorsiflexion of the ankles (Figure 1). The case also shows some signs of facial dysmorphisms including an asymmetric long narrow face with a long thin lip. It is noteworthy to mention that she showed transient anxiety and depression. In this view, her mother had a history of depression and a mild learning disability. The subject also has exhibited genitourinary systems defects. The proband also had a 15-year -old sibling without any symptoms of intellectual disorders, facial dysmorphism or skeletal deformity.

Karyotype analysis was carried out for the proband and her parents. Chromosomal preparations were obtained from Phytohemagglutinin (PHA) stimulated peripheral blood cultures subjected to Giemsa banding at 500 band resolution. Karyotyping was done according to ISCN 2016. Chromosomal analysis of proband revealed 46, XX, del(3)(q29)/16h+ with no evidence of mosaicism, and parental karyotypes were found to be normal (Figure 2; A, B, C). Informed consent was provided and signed by all participants referred to our laboratory in the context of a routine diagnostic procedure.

DISCUSSION

Analysis of chromosome structural abnormalities in a wide spectrum of genetic disorders especially in rare syndromes including 3q29 syndrome with variable clinical phenotypes, through useful methods such as karyotyping, could pave the way for clinical diagnosis. In the present study, we reported a 24-year-old female with 3q29 syndrome presented various clinical abnormalities comprising developmental delay, facial asymmetry, heart defects, asymmetric long narrow face with long thin lip, urinary voiding dysfunction, and passive dorsiflexion of the ankles. Cardiac defects have been previously described in some 3q29 subjects (6,7). Accordingly, our proband was operated on for the cardiac anomaly. So far more than 40 single cases or case series have been reported for 3q29 microdeletion syndrome (8-12).

In most cases, 3q29 syndrome has occurred due to a *de novo* chromosomal rearrangement with no history in their family, while in a rare case autosomal dominant pattern has been reported (13). The clinical manifestations are most common among patients with 3q29 deletion regardless of inheritance or *de novo* rearrangement (10). 3q29 syndrome has been described for the first time in 2001 by Rossi et al. (14). Strikingly, the clinical manifestations of 3q29 syndrome are widely variable including developmental milestone delay, autism, walking delay, gait abnormality, skull shape abnormality, long narrow face, thin upper lip, abnormal teeth, musculoskeletal abnormality, tapered finger, gastroesophageal disorder, heart defects, facial asymmetry, urinary voiding dysfunction, and chronic constipation despite an almost identical deletion size (about 1.6 Mb at position 3q29) among different individuals (15). Notably, some cases were also reported with different sizes of deletion and flanking regions (16). This region is flanked by low copy repeats that may predispose it to rearrangement including non-allelic homologous recombination (15, 16). 3q29 segment contain PAK2 and DLG1 genes which are playing a key role in brain development. In this context, analyzing of most important genes located in 3q29 including DLG1, MUC4, MUC20, TNK2, SLC51A, PCYT1A, TM4SF19, FBXO45, PAK2, PIGX, CEP19, BDH1, and FYTTD1 (17), by Kyoto Encyclopedia of Genes and Genomes (KEGG) available at https://www.genome.jp/kegg/ and GO (gene ontology) available at webserver http:// geneontology indicated that they are mostly involved in neurons -related pathways (Table 1).

Correspondingly, results from Genotype-Tissue Expression (GTEx) (https://gtexportal.org/home/) have revealed that DLG1 is highly expressed in various brain tissues including the brain-cerebellar hemisphere, cerebellum, brain spinal cord, hippocampus, and hypothalamus. GTEX also demonstrated

that PAK2 is remarkably expressed in adipose-visceral, artery coronary, artery tibia, and nerve tibial tissues along with several brain tissues (Figure 3; A and B). Furthermore, the cancer cell line encyclopedia (CCLE) (https://portals.broadinstitute.org/ccle) showed higher expression levels of DLG1 (Figure 4A) in chondrosarcoma, glioma, ovary, mesothelioma, and lung-NSC in comparison with other cell lines. It also has illustrated that PAK2 (Figure 4B) is highly expressed in lymphoma, lung-NSC, breast, and multiple myeloma. Therefore it is not surprising that individuals with 3q29 microdeletion show brain-related developmental disorders including anxiety disorder, autism, schizophrenia, depression, and skull shape abnormality.

On the other hand, very variable clinical features among different patients with 3q29 microdeletion created this hypothesis that different gene SNPs located in the 3q29 region might be responsible for this discrepancy. Therefore, National Center for Biotechnology Information (NCBI) website browser (https://www.ncbi.nlm.nih.gov/) and dbSNP were used to achieve SNPs related to DLG1, FYTTD, and SLC51A. Moreover, analysis of missense SNPs of DLG1, FYTTD1, and SCLC51A via several powerful tools such as SIFT, Polyphen2 have shown that rs1134986, rs34492126, and rs3205525 could probably influence the structure and function of DLG1 and FYTTD while the structure and function of SLC51A were not affected by rs939885 (Table 2). It should be pointed out that mental retardation has been reported in most studies (18, 19). It is noteworthy to mention that brain developmental disorders especially intellectual disability (82%) are the main symptoms that have been reported in most studies rather than other variable clinical manifestations related to 3q29 microdeletion syndrome (10, 13, 18, 20) (Table 3). Furthermore, high nasal bridge (65.9%), speech delay (72%), ocular abnormalities (65%), psychiatric disorder (53%), and delayed walking (42.8%) are the most common phenotypes in patients with 3q29 microdeletion syndrome (10, 18, 6) (Table 3). Notably, a wide spectrum of facial dysmorphism characteristics includes facial asymmetry (26.6%), long narrow face (36%), long philtrum (16%), smooth philtrum (16%), thin upper lip (30.7%), and cleft/ lip/palate and submucous cleft (9%) have been reported in patients presenting 3q29 deletion (Table 3). Moreover, a broad variety of skeletal malformations including long, non-tapering fingers, microcephaly, elongated face, long fingers, joint laxity, high nasal bridge, abnormal teeth, scoliosis, and torsion of the upper body were also reported in some cases but not seen in all patients with 3q29 microdeletion syndrome. Taken together, the most common clinical features reported regarding 3q29 microdeletion syndrome are intellectual disability, psychiatric disorder, speech and walking delay, skeletal deformity, high nasal bridge, microcephaly, and short philtrum.

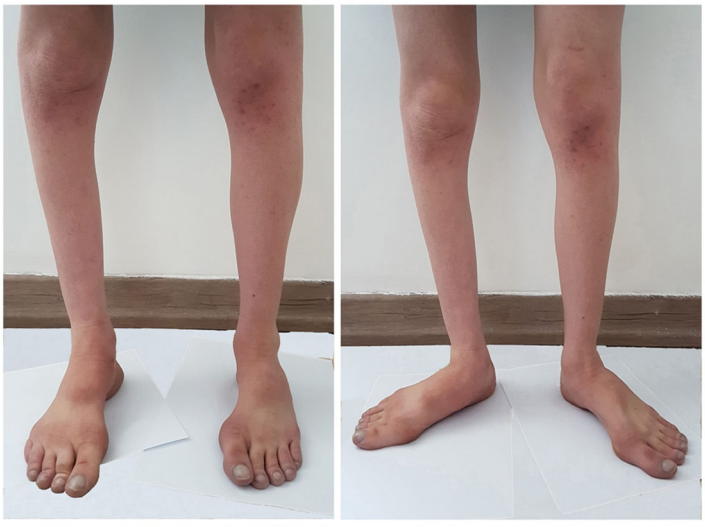

Figure 1. Skeletal deformities of the leg

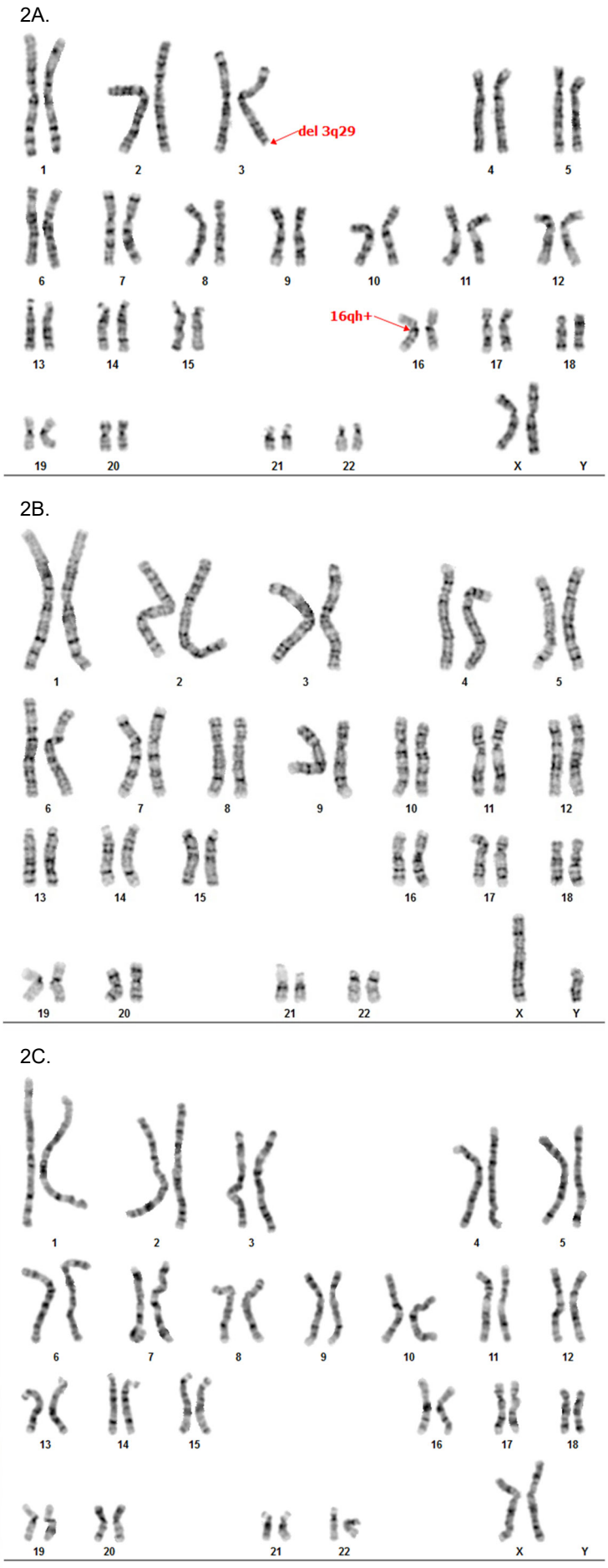

Figure 2: Karyotype of the patient with *denovo* 3q29 microdeletion and her parents. (A) Karyotyping of the case showing 3q29 microdeletion; (B, C) Karyotype of her father and mother showed no deletion in 3q29 region.

Table 1. The biological pathways related to DLG1 and PAKs predicted by KEGG and GO

Gene	KEGG	GO	Gene	KEGG	GO
DLG1	• Hippo signalling pathway • Tight junction • T cell receptor signalling pathway • Human papillomavirus infection • Human T-cell leukaemia virus 1 infection • Viral carcinogenesis	• ionotropic glutamate receptor complex postsynaptic density membrane • chemical synaptic transmission • neuron projection • receptor localization to synapse • neuromuscular junction • cell junction	**FBXO45**	NF	• neuron migration • protein binding • ubiquitin-dependent protein catabolic process • cellular response to DNA damage stimulus • postsynaptic density • protein ubiquitination • cerebral cortex radially oriented cell migration • cerebral cortex tangential migration
MUC4	NF	• stimulatory C-type lectin receptor signalling pathway • ErbB-2 class receptor binding Golgi lumen	***PAK2***	• Axon guidance • MAPK signalling pathway • ErbB signalling pathway • Ras signalling pathway • Focal adhesion • T cell receptor signalling pathway • Regulation of actin cytoskeleton • Pathogenic Escherichia coli infection • Human immunodeficiency virus 1 infection • Renal cell carcinoma	• stimulatory C-type lectin receptor signalling pathway • protein kinase activity • protein serine/threonine kinase activity • protein serine/threonine kinase activity • protein serine/threonine kinase activity • Protein binding
MUC20	NF	• stimulatory C-type lectin receptor signalling pathway • extracellular region • Golgi lumen	**PIGX**	• Glycosylphosphatidylinositol (GPI)-anchor biosynthesis • Metabolic pathways	• endoplasmic reticulum membrane • integral component of membrane • preassembly of GPI anchor in ER membrane
TNK2	NF	• Tyrosine kinase non receptor 2	**CEP19**	NF	• spindle pole • protein binding
SDHAP1	NF	NF	**BDH1**	NF	• 3-hydroxybutyrate dehydrogenase activity • Nucleoplasm • mitochondrion • ketone body biosynthetic process • ketone body catabolic process • oxidation-reduction process • matrix side of mitochondrial inner membrane
SLC5	NF	• protein binding • endoplasmic reticulum membrane • plasma membrane • bile acid transmembrane transporter activity • bile acid and bile salt transport • integral component of membrane • basolateral plasma membrane • bile acid secretion • protein homodimerization activity	**FYTTD1**	NF	• RNA binding • mRNA binding • protein binding • nucleoplasm • mRNA export from nucleus • nuclear speck
PCYT1A	NF	• choline-phosphate cytidylyltransferase activity • protein binding	**MF12**	NF	NF
TM4SF19	NF	• Protein binding	**WDR53**	NF	NF

NF = Not Found

Table 2. Prediction of functional effects of DLG1, FYTTD1 and SCLC51A SNPs on protein structure

Gene ID	SNP ID	MAF	Substitution	Position (GRCh38.p12)	SIFT	SIFT score	Polyphen2	Polyphen2 score	PROVEAN	PROVEAN score	SNAP2	SNAP2 score/ Accuracy	Phd-SNP	Phd-SNP score	PANTHER	PANTHER score	Fathmm
DLG1	1. rs1134986	T=0.1280	R (Arg) > Q (Gln)	chr3:197138371	TOLERATED	0.38	POSSIBLY DAMAGING	0.919	Neutral	-1.831	Effect	85/91	Neutral	3	probably damaging	750	TOLERATED
DLG1	2. rs34492126	A=0.0252	P (Pro) > L (Leu)	chr3:197044642	DELETERIOUS	0.001	PROBABLY DAMAGING	0.997	Deleterious	-8.817	Effect	80/91	Disease	7	probably damaging	1237	TOLERATED
FYTTD1	3. rs3205525	A=0.7520	R (Arg) > H (His)	chr3:197768463	TOLERATED	0.187	BENIGN	0.073	Deleterious	-2.654	Effect	12/59	Neutral	8	possibly damaging	220	TOLERATED
FYTTD1	4. rs7624719	G=0.0879	P (Pro) > A (Ala)	chr3:197755816	TOLERATED	0.248	BENIGN	0.000	Neutral	0.024	Neutral	-27/61	Neutral	9	NA	NA	TOLERATED
SLC51A	5. rs939885	A=0.4569	V (Val) > I (Ile)	chr3:196228891	TOLERATED	0.816	BENIGN	0.000	Neutral	0.101	Neutral	-86/93	Neutral	8	NA	NA	TOLERATED

NA Not Analysed

Table 3: Clinical features of patients with 3q29 microdeletion syndrome from 20 studies

			Our proband	Clinical manifestations reported by other studies																				
Clinical features		**Number of cases reported (%)**	**Manifestations (n)/Case (n)**	**References**	(14)	(19)	(1)	(5)	(20)	(9)	(18)	(16)	(21)	(8)	(22)	(13)	(23)	(24)	(25)	(26)	(27)	(28)	(29)	(6)
Growth/neuro development	Intellectual disability (IQ score ≤75)	37/45 (82%)	1		1/1	1/1	6/6	1/1	1/1	7/7	4/4	0/2	1/1	2/2	0/1	4/4	_	_	1/1	4/4	1/2	1/1	0/4	1/1
	Autism/ autistic features	12/36 (33%)	0/1		_	_	2/6	1/1	_	1/7	0/4	_	_	2/2	1/1	1/4	0/1	_	1/1	_	1/2	1/1	0/4	1/1
	Psychiatric disorder	16/30 (53%)	1		_	_	_	1/1	_	1/7	1/4	_	_	2/2	1/1	2/4	_	1/1	1/1	_	1/2	1/1	2/4	1/1
Developmental regression	Speech delay	29/40 (75%)	1		_	1/1	5/5	1/1	_	3/7	4/4	0/2	1/1	2/2	1/1	3/4	_	3/3	_	0/4	2/2	1/1	_	1/1
	Nasal voice	10/28 (35.7%)	1		_	_	_	1/1	_	1/7	0/4	_	0/1	1/2	0/1	3/4	_	_	_	1/4	1/2	_	_	1/1
	Delayed walking	18/42 (42.8%)	1		_	1/1	2/5	0/1	_	2/7	1/4	0/2	1/1	2/2	0/1	3/4	_	1/1	_	0/4	1/2	1/1	1/4	1/1
	Short stature	10/35 (28.5%)	_		_	0/1	1/6	0/1	1/1	_	2/4	0/1	0/1	2/2	0/1	2/4	_	1/2	_	0/4	1/2	_	0/4	0/1
	Ataxia gait/ gait abnormality	11/26 (42%)	1		_	_	3/6	1/1	_	2/7	_	_	_	1/2	0/1	0/4	0/1	_	1/1	_	_	1/1	_	1/1
Facial dysmorphism	Abnormal skull shape	6/23 (26%)	1		1/1	1/1	2/6	0/1	0/1	_	_	_	0/1	1/2	0/1	0/4	_	_	_	0/4	_	_	_	_
	Brachycephaly	6/25 (24%)	0/1		_	0/1	0/6	0/1	0/1	_	3/4	_	0/1	1/2	0/1	0/4	_	_	_	2/4	_	_	_	1/1
	Microcephaly	21/39 (53.8%)	1		_	0/1	1/5	1/1	1/1	5/7	4/4	_	0/1	1/2	0/1	4/4	_	0/1	_	1/4	_	1/1	0/4	1/1
	Facial asymmetry	8/30 (26.6%)	1		_	0/1	0/6	0/1	0/1	_	0/4	0/1	1/1	2/2	0/1	0/4	_	_	1/1	_	_	1/1	1/4	1/1
	Long narrow face	13/36 (36%)	1		_	0/1	2/6	1/1	1/1	0/7	0/4	0/1	0/1	1/2	1/1	2/4	_	1/1	_	2/4	_	1/1	_	0/1
	Frontal bossing	6/29 (20.6%)	_		_	1/1	1/6	0/1	0/1	_	0/4	1/1	0/1	0/2	0/1	0/4	_	_	_	_	1/2	_	2/4	0/1
	Low-set, posteriorly rotated ears	17/40 (42.5%)	_		_	1/1	1/6	0/1	0/1	4/7	1/4	1/1	0/1	1/2	1/1	0/4	1/1	_	_	4/4	_	1/1	1/4	0/1
	High nasal bridge	29/44 (65.9%)	1		_	0/1	4/6	1/1	0/1	4/7	4/4	0/1	0/1	2/2	1/1	4/4	0/1	_	1/1	4/4	1/2	1/1	1/4	0/1
	Short philtrum	18/36 (50%)	1		_	0/1	6/6	0/1	0/1	0/7	3/4	0/1	0/1	0/2	1/1	4/4	_	_	_	3/4	_	0/1	_	0/1
	Long philtrum	4/25 (16%)	0/1		_	0/1	0/6	0/1	0/1	_	1/4	1/1	0/1	0/2	0/1	0/4	_	_	_	_	_	1/1	_	1/1
	Smooth philtrum	4/25 (16%)	0/1		_	1/1	1/6	0/1	0/1	_	1/4	1/1	0/1	0/2	0/1	0/4	_	_	_	_	_	0/1	_	0/1
	Thin upper lip	8/26 (30.7%)	1		_	0/1	0/6	0/1	0/1	_	4/4	1/1	1/1	0/2	0/1	0/4	_	_	_	_	1/2	_	_	0/1
	Cleft lip/palate/ submucous cleft	3/33 (9%)	_		_	0/1	1/6	0/1	0/1	0/7	0/4	0/1	0/1	0/2	0/1	0/4	1/1	1/1	_	_	0/1	_	_	0/1
	Abnormal teeth	11/39 (28%)	_		_	0/1	0/6	1/1	0/1	2/7	0/4	0/1	0/1	2/2	0/1	0/4	_	0/1	_	1/4	_	_	4/4	1/1
	Ocular abnormalities	13/20 (65%)	_		_	_	_	_	1/1	_	0/4	_	1/1	1/2	0/1	4/4	_	0/1	_	4/4	_	1/1	_	1/1
Musculoskeletal abnormalities	Scoliosis	5/19 (26%)	0/1		_	_	_	0/1	_	_	0/4	_	0/1	1/2	0/1	1/4	_	_	_	2/4	_	_	_	1/1
	Chest cavity deformity	9/35 (25.7%)	_		_	1/1	2/6	0/1	_	1/7	0/4	_	0/1	0/2	0/1	2/4	0/1	1/1	1/1	2/4	_	_	_	1/1
	Joint contractures	6/23 (26%)	1		_	_	0/6	1/1	_	_	0/4	_	0/1	1/2	0/1	2/4	0/1	_	_	_	_	1/1	_	0/1
	Ligamentous laxity	5/35 (14%)	_		_	_	1/6	0/1	_	0/7	0/4	_	0/1	0/2	1/1	0/4	_	_	_	2/4	_	_	1/4	0/1
	Long/tapered fingers	11/33 (33%)	0/1		_	1/1	3/6	1/1	0/1	0/7	0/4	0/1	0/1	2/2	1/1	2/4	_	_	_	_	1/2	_	_	0/1
	Nail hypoplasia	3/23 (13%)	0/1		_	0/1	1/6	0/1	0/1	_	1/4	0/1	0/1	1/2	0/1	0/4	_	_	_	_	_	_	_	_
	Clinodactyly Toes	9/25 (36%)	0/1		_	1/1	1/6	0/1	_	_	3/4	0/1	0/1	1/2	0/1	1/4	_	_	_	_	2/2	_	_	0/1
	Toe syndactyly	2/24 (8.3%)	0/1		_	0/1	0/6	0/1	_	_	0/4	0/1	0/1	0/2	0/1	1/4	1/1	_	_	_	_	_	_	0/1
Gastrointestinal abnormalities	Constipation	4/9 (44%)	_		_	_	_	_	_	_	_	_	_	1/2	1/1	0/4	_	_	_	_	_	1/1	_	1/1
	Hypertrophic pyloric stenosis	2/9 (22%)	1		_	_	_	_	_	_	_	_	1/1	0/2	0/1	0/4	_	_	_	_	_	_	_	_
Genitourinary defects	Urinary voiding dysfunction	2/8 (25%)	1		0/1	_	_	_	_	_	_	_	_	0/2	0/1	0/2	_	1/1	_	_	_	_	_	_
	Hypospadias	3/17 (17.6)	0/1		1/1	_	_	_	_	1/7	_	_	_	0/2	0/1	0/2	_	_	_	1/2	_	_	_	0/1
Denovo		26/39 (72%)	1/1		1/1	1/1	5/5	1/1	1/1	5/8	0/2	0/1	1/1	2/2	1/1	0/3	0/1	1/1	1/1	1/1	2/2	1/1	0/3	1/1
Inherited		13/39 (33%)	0/1		0/1	0/1	0/5	0/1	0/1	3/8	2/2	1/1	0/1	0/2	0/1	3/3	1/1	0/1	0/1	0/1	0/2	0/1	3/3	0/1
Heart defects *(PDA, ASD, and others)*		9/34 (26.4%)	1/1		_	_	_	0/1	_	1/7	1/4	2/2	0/1	0/2	0/1	_	0/1	1/3	_	1/4	1/2	_	0/4	1/1
Deletion size (Mb)		-	NA		NA	NA	1. 5	NA	1.0	1.6	1.5	1.3_ 1.4	1.6	P1: 1.6 P2: 2.1	1.3	1.6	1.5	1.5	1.58	P1: 1.57 P2:. 607 P3: 1.5 P4: 1.59	P1: 1.6 P2: 1.5	1.68	1.6	0.96 2
Genetic testing and/or genomic coordinates		-	Karyotype		Karyotype and FISH	MLPA and FISH	Karyotype and FISH	Karyotype and FISH	Karyotype and FISH	Karyotype and FISH	-	Karyotype and FISH	-	-	-	Microarray	Microarray	Microarray	-	Karyotype and FISH	CGH array, MLPA & Illumina .Sequencing	Microarray	Microarray	SNP array and FISH

DECLARATIONS OF INTEREST

The authors declare that there is no conflict of interest regarding the publication of this article

AUTHOR INFORMATION

Seyed Mokhtar Esmaeilnejad-Ganji, Professor[1, 2]
Alireza Paniri, MSc[3, 4]
Monireh Golpour, PhD[5]
Reza Tabaripour, Assistant Professor[6]
Haleh Akhavan-Niaki, PhD, Professor[3, 4, 7]

[1]Clinical Research Development Center, Shahid Beheshti Hospital, Babol University of Medical Sciences, Babol, Iran
[2]Department of Orthopedics, Babol University of Medical Sciences, Babol, Iran
[3]Genetics Department, Faculty of Medicine, Babol University of Medical Sciences, Babol, Iran
[4]Zoonoses Research Center, Pasteur Institute of Iran, Amol, Iran
[5]Molecular and Cell Biology Research Center, Student Research Committee, Faculty of Medicine, Mazandaran University of Medical Sciences, Sari, Iran
[6]Department of Cellular and Molecular Biology, Babol Branch, Islamic Azad University, Babol, Iran
[7]Akhavan-Niaki Genetics Laboratory, Babol, Iran

Correspondance: Haleh Akhavan-Niaki
Email: halehakhavan@yahoo.com

REFERENCES

1. Willatt L, Cox J, Barber J, et al. 3q29 microdeletion syndrome: clinical and molecular characterization of a new syndrome. *Am J Hum Genet A* 2005; 77(1): 154-160.
2. https://ghr.nlm.nih.gov/condition/3q29-microdeletion-syndrome. 2020.
3. Città S, Buono S, Greco D, et al. 3q29 microdeletion syndrome: Cognitive and behavioral phenotype in four patients. *Am J Hum Genet* 2013; 161(12): 3018-3022.
4. Bouman A, Weiss M, Jansen S, et al. An interstitial de-novo microdeletion of 3q26. 33q27. 3 causing severe intrauterine growth retardation. *Clin Dysmorphol* 2015; 24 (2): 68-74.
5. Baynam G, Goldblatt J, Townshend S. A case of 3q29 microdeletion with novel features and a review of cytogenetically visible terminal 3q deletions. *Clin Dysmorphol* 2006; 15(3): 145-148.
6. Emandi AC, Dobrescu AI, Doros G, et al. A novel 3q29 deletion in association with developmental delay and heart malformation - case report with literature review. *Front Pediatr* 2019; 8(7): 270.
7. Li F, Lisi EC, Wohler ES ,et al. 3q29 interstitial microdeletion syndrome: an inherited case associated with cardiac defect and normal cognition. *Eur J Med Genet* 2009; 52(5): 349-352.
8. Quintero-Rivera F, Sharifi-Hannauer P, Martinez-Agosto JA. Autistic and psychiatric findings associated with the 3q29 microdeletion syndrome: case report and review. *Am J Hum Genet* 2010; 152(10): 2459-2467.
9. Glassford MR, Rosenfeld JA, Freedman AA, et al. Novel features of 3q29 deletion syndrome: results from the 3q29 registry. *Am J Hum Genet A* 2016; 170(4): 999-1006.
10. Ballif BC, Theisen A, Coppinger J, et al. Expanding the clinical phenotype of the 3q29 microdeletion syndrome and characterization of the reciprocal microduplication. *Mol Cytogenet* 2008; 1(1): 8.
11. Pollak RM, Murphy MM, Epstein MP, et al. Neuropsychiatric phenotypes and a distinct constellation of ASD features in 3q29 deletion syndrome: results from the 3q29 registry. *Mol Autism* 2019; 10(1):30.
12. Baba M, Yokoyama K, Seiriki K, et al. Psychiatric-disorder -related behavioral phenotypes and cortical hyperactivity in a mouse model of 3q29 deletion syndrome. *Neuropsychopharmacology* 2019; 44(12): 2125-2135.
13. Clayton-Smith J, Giblin C, Smith RA, et al. Familial 3q29 microdeletion syndrome providing further evidence of involvement of the 3q29 region in bipolar disorder. *Clin Dysmorphol* 2010; 19(3): 128-132.
14. Rossi E, Piccini F, Zollino M, et al. Cryptic telomeric rearrangements in subjects with mental retardation associated with dysmorphism and congenital malformations. *J Med Genet* 2001; 38(6): 417-420.
15. Cox DM, Butler MG. A clinical case report and literature review of the 3q29 microdeletion syndrome. *Clin Dysmorphol* 2015; 24(3): 89-94.
16. Li F, Lisi EC, Wohler ES, et al. 3q29 interstitial microdeletion syndrome: an inherited case associated with cardiac defect and normal cognition. *Eur J Med Genet* 2009; 52(5): 349-352.
17. Rutkowski TP, Purcell RH, Pollak RM, et al. Behavioral changes and growth deficits in a CRISPR engineered mouse model of the schizophrenia-associated 3q29 deletion. *Mol Psychiatry* 2021; 26(3): 772-783.
18. Digilio MC, Bernardini L, Mingarelli R, et al. 3q29 Microdeletion: a mental retardation disorder unassociated with a recognizable phenotype in two mother–daughter pairs. *Am J Hum Genet* 2009; 149(8): 1777-1781.
19. Koolen D, Nillesen W, Versteeg M, et al. Screening for subtelomeric rearrangements in 210 patients with unexplained mental retardation using multiplex ligation dependent probe amplification (MLPA). *J Med Genet* 2004; 41(12): 892-899.
20. Krepischi-Santos A, Vianna-Morgante A, Jehee F, Passos -Bueno M, et al. Whole-genome array-CGH screening in undiagnosed syndromic patients: old syndromes revisited and new alterations. *Cytogenet Genome Res* 2006; 115(3-4): 254-261.
21. Tyshchenko N, Hackmann K, Gerlach E-M,et al. 1.6 Mb deletion in chromosome band 3q29 associated with eye abnormalities. *Eur J Med Genet* 2009; 52(2-3):1 28-30
22. Cobb W, Anderson A, Turner C,et al. 1.3 Mb de novo deletion in chromosome band 3q29 associated with normal intelligence in a child. *Eur J Med Genet* 2010; 53 (6): 415-418.
23. Petrin AL, Daack-Hirsch S, L'heureux J. A case of 3q29 microdeletion syndrome involving oral cleft inherited from a nonaffected mosaic parent: molecular analysis and ethical implications. *Cleft Palate Craniofac J* 2011; 48(2): 222-230.
24. Dasouki MJ, Lushington GH, Hovanes K,et al. The 3q29 microdeletion syndrome: report of three new unrelated patients and in silico “RNA binding” analysis of the 3q29 region. *Am J Hum Genet A* 2011;155(7): 1654-1660.
25. Sagar A, Bishop JR, Tessman DC,et al. Co-occurrence of autism, childhood psychosis, and intellectual disability associated with a de novo 3q29 microdeletion. *Am J Hum Genet A* 2013;161(4): 845-849
26. Città S, Buono S, Greco D, et al. 3q29 microdeletion syndrome: Cognitive and behavioral phenotype in four patients. *Am J Hum Genet A* 2013; 161(12): 3018-3022
27. Malt EA, Juhasz K, Frengen A, et al. Neuropsychiatric phenotype in relation to gene variants in the hemizygous allele in 3q29 deletion carriers: A case series. *Mol Genet Genomic Med* 2019; 7(9): e889
28. Kaur H, Thom RP, Neumeyer AM, et al. Paroxysmal oculogyric dystonia associated with a de novo 3q29 microdeletion. *Psychiatr Genet* 2020; 30(4): 119-123.
29. Murphy MM, Burrell TL, Cubells JF, et al. Comprehensive phenotyping of neuropsychiatric traits in a multiplex 3q29 deletion family: a case report. *BMC Psychiatry.* 2020; 20 (1): 1-10.