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ORIGINAL ARTICLE

Diagnostic yield of the chromosomal microarray analysis in turkish patients with unexplained development delay/ıntellectual disability(ID), autism spectrum disorders and/or multiple congenital anomalies and new clinical findings

Nejmiye Akkus[1] · **Pelin Ozyavuz Cubuk**[2]

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Abstract

Background Chromosomal microarray analysis is an essential tool for copy number variants detection in patients with unexplained developmental delay/intellectual disability, autism spectrum disorders, and multiple congenital anomalies. The study aims to determine the clinical significance of chromosomal microarray analysis in this patient group. Another crucial aspect is the evaluation of copy number variants detected in terms of the diagnosis of patients.

Methods and results A Chromosomal microarray analysis was was conducted on a total of 1227 patients and phenotype-associated etiological diagnosis was established in 135 patients. Phenotype-associated copy number variants were detected in 11% of patients. Among these, 77 patients 77 (57%, 77/135) were diagnosed with well-recognized genetic syndromes and phenotype-associated copy number variants were found in 58 patients (42.9%, 58/135). The study was designed to collect data of patients in Kocaeli Derince Training and Research Hospital retrospectively. In our study, we examined 135 cases with clinically significant copy number variability among all patients.

Conclusions In this study, chromosomal microarray analysis revealed pathogenic de novo copy number variants with new clinical features. Chromosomal microarray analysis in the Turkish population has been reported in the largest patient cohort to date.

Keywords Chromosomal microarray analysis · Developmental delay/intellectual disability · Microdeletion and microduplication syndromes

Introduction

Chromosomal microarray analysis (CMA) has been the first-tier test for patients presenting with unexplained developmental delay/intellectual disability (DD/ID), autism spectrum disorders (ASD) and multiple congenital anomalies (MCA), since 2010. [1, 6–11].

DD/ID are clinically heterogeneous neurodevelopmental disorders seen in 1–3% of children [9]. Thus, genetic testing plays an important role in evaluating patients with DD/ID, ASD, and MCA, however, etiology is still not defined in all patients. Microarray analysis has increased the detection rate of chromosomal imbalances in the human genome, enabling the diagnosis of syndromic phenotypes with previously unknown etiologies. CMA detects microdeletion and microduplication syndromes in this group with a high diagnostic yield [11, 12]. In addition, with the use of high-resolution microarray analyses, it is possible to identify new regions whose copy number changes have not been associated with any phenotype before.

ASD is a complex and genetically heterogeneous disorder, characterized by social communication deficits and interaction as well as restricted, stereotypic behaviors. A recent study estimated that the prevalence is about 1–2% [2,

✉ Nejmiye Akkus
drnejmiyeakkus@gmail.com

Pelin Ozyavuz Cubuk
ozyavuzpelin@gmail.com

[1] Department of Medical Genetics, Faculty of Medicine, Tokat Gaziosmanpasa University, Tokat, Türkiye

[2] Department of Medical Genetics, Ministry of Health Haseki Training and Research Hospital, Istanbul, Türkiye

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3]. Previous studies have shown that genetic factors contribute to the diagnosis of ASD [4, 5].

On the other hand, some syndromes been rarely reported despite their potential for diagnosis, such as the Bosch-Boonstra-Schaaf Optic Atrophy Syndrome (BBSOAS; MIM #615,722), 18p monosomy syndrome, 9p duplication syndrome (ORPHA:236), 6q terminal deletion syndrome (ORPHA:75,857), 2q33.1 microdeletion syndrome, and 6q27 terminal deletion syndrome.

The CMA studies plays a significant role in investigating the genetic etiology and identifying new syndromes in patients diagnosed with DD/ID, ASD, and MCA [6–8]. The study aimed to identify CNVs and clinical phenotypes by determining the clinical efficiency of CMAs in evaluating DD/ID, ASD, and MCA in Turkish patients.

Materials and methods

In this study, 1227 patients with DD, ASD, and MCA who were consulted by the Department of Medical Genetics at the Health Sciences University Kocaeli Derince Training and Research Hospital were included.

Ethical committee approval for the study was obtained from the Kocaeli Derince Training and Research Hospital Ethical Board (2021–53).

In this study, we presented the CNVs we detected in 135 patients with DD, ASD, and MCA, with or without accompanying dysmorphic features, growth disorder, or epilepsy, and correlated them with the clinical findings. After written informed consents were obtained from the parents of the patients, DNA was isolated from peripheral blood. Microarray analysis was performed using CytoScan Optima, Affimetrix® chips according to the manufacturer's protocol and the data was analyzed by Chromosome Analysis Suite (ChAS) 3.1 Thermo Fisher Scientific®. Copy number variations (CNVs) with a gene size greater than 100 kb and represented by a minimum of 25 probes were considered in variant calling.

Database of Genomic Variants (DGV, http://projects.tcag.ca/variation), Database of Chromosomal Imbalance and Phenotype in Humans Ensembl Resources (DECIPHER, https://decipher.sanger.ac.uk), PubMed (https://www.ncbi.nlm.nih.gov/pubmed), Online Mendelian Inheritance of Man (OMIM; https://www.ncbi. nlm. nih.gov/omim), ClinVar (https:// www. ncbi. nlm. nih. gov/ clinv ar) and in-house database of Haseki Genetic Diagnosis Center were used to identify the CNVs with three classes: variants of uncertain clinical significance (VUS), likely pathogenic, and pathogenic.

In this study, we examined cases with clinically relevant CNVs, categorized as "pathogenic", "likely pathogenic", or "VUS" variants by assessing the diagnostic efficiency of microarray analysis, a frequently used method, in diagnosing patients with DD/ID, ASD, and MCA, according to the American College of Medical Genetics and Genomics guidelines (ACMG) and ClinGen [13].

A retrospective study was conducted on patients with DD/ID, ASD, and MCA within the period between January 1, 2017 and March 30, 2021. A total of 1227 patients with DD/ID, ASD, and MCA were examined using the CMA test. Male individuals underwent conventional karyotyping and Fragile X analysis before introducing microarray analysis. In this study, we analyzed the data from routine microarray analysis performed on patients admitted to the outpatient clinic of the Department of Medical Genetics who were diagnosed with DD/ID, ASD, and MCA.

Results

The results of 1227 patients, 701 male and 526 female, who underwent CMA in the genetics outpatient clinic were evaluated and phenotype-associated CNVs were found in 58 (42.9%, 58/135) patients. Furthermore, 77 out of 135 patients (57%) were diagnosed with well-recognized genetic syndromes via the OMIM database (Table 1). Demographic information and clinical features of the patients are shown in Tables 1, 2, and 3.

Phenotype-associated CNV was detected in 58 patients, where 25 patients were classified as pathogenic CNV (Table 2) and 33 patients had CNV of uncertain clinical significance (Table 3). The diagnosis of well-recognized genetic syndromes was achieved in 77 patients (Table 1). The patients are listed in Tables 1, 2, and 3.

The number and percentage of patients diagnosed with a well-known genetic syndrome are indicated in Table 4. Among the well-known genetic syndrome diagnoses, 22q11.2 microdeletion syndrome was the most common, as it was observed in 4 patients. On the other hand, 3 patients were diagnosed with 16p13.11 microdeletion syndrome, 3 patients were diagnosed with 16p13.11 microduplication syndrome, 3 patients were diagnosed with Williams-Beuren syndrome, and 3 patients were diagnosed with Wolf-Hirschhorn syndrome (Table 4). Table 5 shows the number and percentage of patients diagnosed with multiple CMA findings.

On the other hand, our study identified 16 ASD patients with phenotype-related CNVs including 8 patients with well-recognized genetic CNVs and 8 patients with uncertain CNVs in ASD. The well-known genetic syndromes identified in 8 patients with ASD were; Joubert syndrome (patient 1), Xq28 microduplication syndrome (patient 4), Klinefelter syndrome (patient 17), Coffın-Siris Syndrome 6 (patient 25), 15q13.3 microdeletion syndrome (patient 28), 16p13.11 microduplication syndrome (patient 48), 7q11.23

Table 1 Patients with a well-known genetic syndromes

Case	Age/Sex	Region	Known syndrome	OMIM numbers	Type/Size	Critical genes or region	OMIM genes	Karyotype	Major clinical findings	Facial dysmorphology	Inheritance
1A	15/M	arr[hg19] 2q13(110,874,326_110,983,418)x1	Joubert Syndrome		Del 109kbp	*NPHP1, LINC00*116			Severe developmental delay/ıntellectual disability (DD/ID), autism	Short philtrum, deeply set eyes, hypotelorism	N.D.[a]
2A	10/F	arr[hg19] 4p16.3(68,345_3,719,026)x1	Wolf-Hirschhorn Syndrome	#194190	Del 3,651kbp	70	70		ID, global DD, precocious, MVP, MY	Small facial, hypotelorism, low-set ears, exophthalmos, prominent kyphosis	N.D
3A	5/F	arr[hg19] 3q27 .3q29(186,838,656_197,851,986)x3, 18q22.3q23(72,196,741_78,014,123) x1	18q23 Deletion Syndrome		Dup 11,013 kbp Del 5,817 kbp		Dup 120 Del 33		DD/ID		de novo
4A	10/M	arr[hg19] 15q22.2(62,860,242_63,406,863)x3, Xq28(153,567,758_153,963,756)x2	Xq28 Microduplication Syndrome	#300815	Dup 547kbp Dup 396kbp	15q22.2 *MGC15*885, *TLN2, MIR190A, TPM1* Xq28 (25)			Autism		N.D
5A	1/M	arr[hg19] 16q12 .1q12.2(49,943,803_55,223,146)x1	16q12 Microdeletion Syndrome		Del 5,279kbp	*CYLD, NOD2, SALL1*	36		DD/ID, hypotonia, VSD,	Retroverted low-set ears, left simple ear, wide nasal root, deeply set eyes, hypertelorism, strabismus	N.D
6A	9/M	arr[hg19] 15q13 .2q13.3(31,073,668_32,915,723)x1	15q13.3 Microdeletion Syndrome	#612001	Del 1,842kbp	*CHRNA*7			ID, global DD, PS, aortic regurgitation, bicuspid aortic valve	Long triangular face, high nasal bridge, prominent ears, pectus excavatum	N.D
7A	5/F	arr[hg19] 10p15.3p14(100,026_11,950,322)x1	10p15.3 Microdeletion Syndrome		Del 11,850kbp	*ZMYND*11 (OMIM#608668) *DIP2C* (OMIM# 611380) *WDR37* (OMIM#618586)			ID, global DD, microcephaly, neonatal hypotonia	Synophrosis, highly arched eyebrow structure, depressed nasal ridge, short philtrum, low-set ear, 2-3 syndactyly on the feet, long eyelashes	N.D
8A	4/M	arr[hg19] 10q22 .3q23.2(81,646,459_88,931,737)x1	10q22.3-q23.2 Deletion Syndrome	#612242	Del 7,285 kbp	47			DD/ID, corpus callosum hypoplasia, PS, perimembranous VSD		N.D
9A	1/F	arr[hg19] 5p15.33(919,496_1,285,604) x3, 9q34.3(140,489,625_140,798,298) x1	Kleefstra Syndrome	#610253	Dup 366kbp Del 309kbp	*EHMT1*	Dup:8 Del:7		Neonatal hypotonia, DD/ID, hypotonia	CMRI: normal	N.D
10A	4/M	arr[hg19] 5q14.3q15(92,186,058_93,195,389) x1	Bosch-Boonstra-Schaaf Optic Atrophy Syndrome	#615722	Del 1,009kbp	*NR2F1*	6		ID, global DD, short stature	Triangular face, deeply set eyes, short philtrum	N.D

Table 1 (continued)

Case	Age/Sex	Region	Known syndrome	OMIM numbers	Type/Size	Critical genes or region	OMIM genes	Karyotype	Major clinical findings	Facial dysmorphology	Inheritance
11A	11/F	arr[hg19] 17p11.2(16,783,645_20,392,074)x1	Smith Magenis Syndrome	#182290	Del 3,608kbp	*RAI1*	71	46,XX,del(17)(p11.2p11.2)	DD/ID, aggressiveness, self destructive behavior		N.D
12A	7/F	arr[hg19] 15q11 .2q13.1(23,635,046_28,828,168)x1	Prader-Willi/ Angelman Syndrome	#105830	Del 5,193kbp		115		DD/ID, microcephaly, epilepsy, aggressiveness, self destructive behavior	Unable to walk without support, puppet-like gait, wide mouth, pes cavus	N.D
13	13/M	arr[hg19] 1q21 .1q21.2(145,927,661_147,883,764)x1	1q21.1 Deletion Syndrome	#612474	Del 1,959kbp		25		DD/ID, epilepsy, occipital encephalomalacia	Prominent ears, narrow forehead, occipital encephalomalacia	N.D
14A	2/M	arr[hg19] Xq22.2(102,995,019_103,162,012)x0	Pelizaeus-Merzbacher Syndrome	#312080	Del 167kbp	*PLP1*			DD/ID, severe hypotonia		N.D
15A	0/M	arr[hg19] 16p13. 11p12.3(14,913,788_16,858,308)x3	16p13.11 Recurrent Microduplication Syndrome		Del 1,945kbp		45		N/A		N.D
16A	5/M	arr[hg19] 1p36. 33p36.32(1,908,648_2,568,425)x1	1p36 Deletion Syndrome	#607872	Del 660kbp	*GABRD, SKI*	18		DD/ID, microcephaly, ASD	Hypotelorism, high nasal bridge, de novo synophrosis, deeply set eyes, short philtrum, long face	
17A	6/M	arr(X)x2,(Y)x1	Klinefelter Syndrome					47,XXY	Autism		N.D
18A	8/F	arr[hg19] Xq22 .1q23(100,213,231_109,412,333)x3	Pelizaeus-Merzbacher Syndrome	#312080	Del 9,199kbp	*PLP1*	102		DD/ID		N.D
19A	7/M	arr[hg19] 17p11.2(16,783,645_20,238,524)x1	Smith Magenis Syndrome	#182290	Del 3,455kbp	RAI1 (#607642)	69	46,XY,del(17)(p11.2p11.2)	DD/ID, learning disability, speech delay, aggressiveness, self destructive behavior		N.D
20A	11/F	arr[hg19] 15q11 .2q13.1(22,770,421_28,660,038)x1	Prader-Willi/ Angelman Syndrome	#105830	Del 5,890kbp	*SNRPN, UBE3A*	125		DD/ID, epilepsy, stereotypical clapping movements	Hypetelorism, high nasal bridge	N.D

Table 1 (continued)

Case	Age/Sex	Region	Known syndrome	OMIM numbers	Type/Size	Critical genes or region	OMIM genes	Karyotype	Major clinical findings	Facial dysmorphology	Inheritance
21A	5/F	arr[hg19] 17p11.2q11.2(19242466_27194634)x3, 17q22q23.1(51395969_58064804)x3, 17q23.2(58946690_60116600)x3, 17q24.1(62998022_64158655)x3	Potocki-Lupski Syndrome	#610883	Dup 7,952kbp 1,170kbp 1,161kbp		85 70 10	mos 47,XX+mar[19]/46,XX[31]	Epilepsy, corpus callosum hypoplasia, cerebral atrophy	Hypertelorism, bilateral epicanthus, depressed nasal ridge, short filtrum, narrow forehead, MRI: inferior vermis hypoplasic, 4th ventricle-associated cyst, decrease in deep and white matter volume	N.D
22A	0/F	arr[hg19] 13q33.3q34(108420793_115107733)x1, Xp21.1(31620837_31844448)x1	Duchanne muscular dystrophy	#310200	Del 6,687kbp 224kbp		77		Microcephaly	Case 35A mother Case 36A father	
23A	12/M	arr[hg19] 15q11.2q13.1(22770421_28516084)x4	15q11 Tetrasomy Syndrome		Dup 5,746kbp		122		DD/ID, epilepsy	Prominent ears	de novo
24A	0/F	arr[hg19] 2p16.3p16.1(50443907_55676153)x3, 4p16.3p16.1(68345_10811651)x1	Wolf Hirschhorn Syndrome	#194190	Dup 5,232kbp Del 10,743kbp		Dup 25 Del 130	46,XX,del(4)(p15.3)	Microcephaly, ID, epilepsy, severe DD, hypotonia	Downslanted palpebral fissures, bilateral simian line, 2-3 syndactyly in feet, short philtrum, metopic depression, triangular face, micrognathia	N.D
25A	3/M	arr[hg19] 12q12q13.11(46192356_46833605)x3	Coffın-Sırıs syndrome 6	#617808	Dup 641 kbp	*ARID2*	5		Autism	Triangular face, prominent ears, macrocephaly	N.D
26A	7/M	arr[hg19] 22q13.31q13.33(47195273_51197838)x1	Phelan-McDermid Syndrome	#606232	Del 4,003kbp	*SHANK3*	51	46, XY,r(22)p13q13.3	ID, severe DD, hypotonia		N.D
27A	2/M	arr[hg19] Xp22.33 or Yp11.32(513368_944608 or 463368_894608)x1	Leri Weill Diskondrosteozis (LWD)	#127300	Del 431kbp	SHOX	1		Short stature		N.D
28A	10/M	arr[hg19] 15q13.2q13.3(31154980_32914239)x1	15q13.3 Microdeletion Syndrome	#612001	Del 1759 kbp		19		Autism, DD/ID, esophageal atresia	Feeding with gastrostomy, eating and swallowing dysfunction	N.D
29A	2/F	arr[hg19] 9p24.3p13.1(203861_38787480)x3	Nicolaides–baraitser syndrome	#601358	Dup 38,584kbp	*SMARCA2*	225	46,XX,add(15)(p11.2)	DD/ID, hypotonia, epilepsy, microcephaly, ASD	Scaphocephaly, malar hypoplasia, microphthalmia,hypoplasic ala nasi, short philtrum, right palmar crease single transverse	N.D
30A	2/F	arr[hg19] 7q11.23(72765457_74257046)x1	Williams-Beuren Syndrome	#194050	Del 1,492kbp	*ELN* (#130160)	29		DD/ID, hypotonia, PS	Hypertelorism, depressed nasal ridge, epicanthus, insufficient weight gain, long filtrum	N.D
31A	2/M	arr[hg19] 22q11.21(18917030_21804886)x4	22q11.2 Microduplication Syndrome	#608363	Dup 2,888kbp		79		DD/ID, corpus callosum hypoplasia	Hypospadias, cryptorchidism, hypertelorism, strabismus, broad nasal bridge, antevert nares, long filtrum	N.D
32A	11/M	arr[hg19] 9q34.3(139711692_141020389)x1	9q34.3 Deletion Syndrome (Kleefstra syndrome-1)	#610253	Del 1,309kbp	*EHMT1*			ID, severe DD, epilepsy, hypotonia	Coarse face, open mouth	N.D

Table 1 (continued)

Case	Age/Sex	Region	Known syndrome	OMIM numbers	Type/Size	Critical genes or region	OMIM genes	Karyotype	Major clinical findings	Facial dysmorphology	Inheritance
33A	5/F	arr[hg19] 18p11.32p11.21(136226_15124170) x1	18p Monosomy Syndrome (ORPHA:1598)		Del 14,988kbp		109		DD/ID	Broad nasal bridge, epicanthus, facial asymmetry, long philtrum	N.D
34A	7/M	arr[hg19] 4p16.3(68345_2054373)x1	Wolf Hirschhorn Syndrome	#194190	Del 1,986kbp		45		DD/ID, epilepsy, neonatal hypotonia	Strabismus, short philtrum,	N.D
35A	26/F	arr[hg19] Xp21.1(31620837_31824850) x1	DMD		Del 204kbp				Segregation analysis	22A's mother	N.D
36A	31/M	arr[hg19] 3p12.2p12.1(81619 587_83704233)x1	Glucogen Storage Disease type-4	#232500	Del 2,085kbp	*GBE1*			Segregation analysis	22A's father	N.D
37A	6/F	arr[hg19] 16p13.11(15241280_16521281)x3	16p13.11 Recurrent Microduplication Syndrome		Dup 1,280kbp		35		ID, severe DD		Mother balanced translocation carrier
38A	15/F	arr[hg19] 1q21 .1q21.2(146,581,117_147,393,549)x3	1q21.1 Microduplication Syndrome	#612475	Dup 812kbp		10		Short stature		N.D
39A	11/F	arr[hg19] 15q11.2(22,770,421_23,276,605)x1	Chromosome 15q11.2 deletion syndrome	#615656	Del 506 kbp	TUBGCP, CYFIP1,NIPA2,IPA1, LOC283683,WHAMMP3, GOLGA8IP	7		Behavioral problems		N.D
40A	2/M	arr[hg19] 16p11.2(29567295_30226930)x1	16p11.2 Microdeletion Syndrome	#611913	Del 660kbp	*PRRT2*	43		DD	Blepharophimosis, synophrosis, bilateral ptosis, long philtrum, depressed nasal ridge, antevert nares, scalp hair, sparse	N.D
41A	13/F	arr[hg19] 3q13.31(114237032_114952404) x3, (X)x1	Primrose Syndrome/ Turner Syndrome	#259050	Dup 715kbp	*ZBTB20*	5		Short stature		N.D
42A	2/M	arr[hg19] 8p23.1p21.1(11935023_27551740) x3, 8p23.3p23.1(158048_6982980)x1	Monosomy in distal 8p Syndrome		Dup 15,617kbp Del 6,825 kbp		Dup 134 Del 46	46,XY,der(8)(8p23.3::8p23.1→8p 21.1::8p23.1→8qter)	DD/ID, hypotonia, corpus callosum agenesis	Macrocephaly, prominent ears	de novo
43A	19/M	arr[hg19] 16q23.1q23.3(78961206_83310923) x1	Ayme-Gripp Syndrome	#601088	Del 4,350kbp	*MAF* gene (#177075)	30		DD/ID, epielpsy, congenital catarct, growth hormone deficiency	Scoliosis 12 degrees, high nasal bridge, short philtrum, blepharophimosis, arachnodactyly	de novo

Table 1 (continued)

Case	Age/Sex	Region	Known syndrome	OMIM numbers	Type/Size	Critical genes or region	OMIM genes	Karyotype	Major clinical findings	Facial dysmorphology	Inheritance
44A	17/M	arr[hg19] 22q11.21(18917030_21928916)x1, 22q11.22q11.23(22998049_24933069)x3	22q11.2 Microdeletion Syndrome	#611867	Del 3,012kbp Dup 1,935kbp		Del 81 Dup 44		DD/ID, tetralogy of fallot, microcephaly	Blepharophimosis, short philtrum, eyebrow, highly arched, low-set prominent ear, macrodontia CMRI: cerebral and cerebellar atrophy	N.D
45A	7/M	arr[hg19] 22q11.21(18917030_21082033)x1	22q11.2 Microdeletion Syndrome	#611867	Del 2,165kbp		57		DD/ID, short stature, learning disability	Micropenis, small hands, feet, hypospadias	Father had deletion
46A	0/M	arr[hg19] 9p24.3p23(203861_13750430)x3, 9p21.3p13.2(21931895_36793445)x3, 9p23p21.3(13759928_21928300)x4, 9p13.2p13.1(36809550_38787480)x4	9p Duplication syndrome (ORPHA:236)		Dup 13,547kbp 14,862kbp 8,168kbp 1,978kbp		55 130 53 22	47,XY,+i(9)(p10)			N.D
47A	14/M	arr[hg19] 16p13.11(14866283_16475181)x1	16p13.11 Microdeletion Syndrome		Del 1,609kbp		45		DD/ID, learning disability, speech delay, short stature	Long face, prominent ears, long philtrum	de novo
48A	7/M	16p13.11(15450289_16521281)x3, Xp22.31(6486489_8086425)x2	16p13.11 Microduplication Syndrome		Dup 1,071kbp		34		Autism, epilepsy		de novo
49A	2/M	arr[hg19] 12p13.33p13.31(173786_5749168)x1, 17p13.3(525_3057413)x3	12p13.33 Deletion Syndrome/ 17p13.3 Duplication Syndrome		Del 5,575kbp Dup 3,057kbp	*YWHAE, CRK, PAFAH1B1*	Del 63 Dup 65		DD/ID, learning disability, corpus callosum hypoplasia	Synophrosis, hypotelorism	de novo
50A	12/F	arr[hg19] 17p12(14114279_15475087)x3, 21q11.2q22.3(15500149_48097372)x3	Down syndrome/ CMT Syndrome		Dup 1361 kbp 32597 kbp	*PMP22* gene			DD/ID, learning disability		N.D
51A	2/F	arr[hg19] 6q27(166528912_170919482)x1	6q terminal Deletion Syndrome (ORPHA:75857)		Del 4,391kbp		56		DD/ID, hypotonia, feeding problems	Prominent ear, short philtrum, strabismus	de novo
52A	3/M	arr[hg19] 15q11.2q13.1(23654293_28456373)x1	Prader-Willi/ Angelman Syndrome	#105830	Del 4,802kbp		111		ID, severe DD, lack of speech, corpus callosum hypoplasia, repetitive stereotypical movements	Triangular face, gait disturbance, blond, macrostomia	N.D

Table 1 (continued)

Case	Age/Sex	Region	Known syndrome	OMIM numbers	Type/Size	Critical genes or region	OMIM genes	Karyotype	Major clinical findings	Facial dysmorphology	Inheritance
53A	1/F	arr[hg19] 22q11.21(18917030_21465662)x1	22q11.2 Microdeletion syndrome	#611867	Del 2,549kbp		72		DD, tetralogy of fallot, hypotonia, right hemiparesis	Broad nasal bride, fascial asymmetry, broad forehead	N.D
54A	4/M	arr[hg19] 7q11.23(72765457_74175640)x1	Williams-beuren syndrome	#194050	Del 1,410kbp	*ELN* (#130160)	27		DD/ID, PS, supravalvular aortic stenosis	Small face, macrosomia, depressed nasal root, prolonged colic, chronic constipation, long philtrum, small chin	N.D
55A	0/F	arr[hg19] 10q26.3(133051452_135427143)x1, 12q24.11q24.33(110988885_133777902)x3	Impaired intellectual development and distinctive Facial features with or without cardiac defects; MRFACD	#616789	Del 2,376kbp Dup 22,789kbp	*MED13L* (#608771)	Del 38 Dup 262	46,XX,der(10)(10pterm→10q26::?)	DD, VSD, ASD, PDA, hypotonia, hypothyroidism, hyperparathyroidism	Talipes valgus, long eyelashes, antevert nares, prominent nose, short philtrum, palmar crease single transverse, left hand flexor contracture, low-set ears, hairline low posterior, short neck	N.D
56A	3/F	arr[hg19] 16p13.11(16,267,967_16,391,910)x1	16p13.11 Microdeletion syndrome		Del 124kbp		2		DD/ID	Long face, broad nasal bridge, short philtrum	de novo
57A	0/F	arr[hg19] 15q24.2(75,567,134_75,898,596)x1	15q24 microdeletion syndrome	#613406	Del 331kbp		8		VSD, PDA		de novo
58A	4/F	arr[hg19] 22q11.21(18,917,030_21,465,662)x1	22q11.2 Microdeletion syndrome	#611867	Del 2,549kbp		73		PS, truncus arteriosis, right aortic arch, aortic stenosis		N.D
59A	18/M	arr[hg19] 15q24.2q24.3(75,567,134_78,210,123)x1	15q24 Microdeletion syndrome	#613406	Del 2,643kbp		36		DD/ID, epilepsy, obesity		N.D
60A	1/F	arr[hg19] 7q11.23(72,225,441_74,154,634)x1	Williams-beuren syndrome	#194050	Del 1,929kbp				PS, hypothyroidism	Macrostomia, long philtrum	N.D
61A	0/M	arr[hg19] 17p13.3p13.2(2,474,928_3,444,224)x1	Miller dieker syndrome	#247200	Del 969kbp	*PAFAH1B1*(#6015459	22		DD/ID, hypotonia, epilepsy, lissencephaly	Strabismus	N.D
62A	3/M	arr[hg19] 7q11.23(72,701,768_74,175,640)x3	7q11.23 Duplication syndrome	#609757	Dup 1,474kbp		29		Autism		de novo
63A	0/M	arr[hg19] 18q21.31q23(54,334,985_78,014,123)x1	18q Deletion syndrome	#601808	Del 23,679kbp		115		İnguinal hernia		N.D
64A	3/M	arr(8)x3[0.32]	Mosaic trisomy 8(Warkany Syndrome 2)						Autism		de novo
65A	2/F	arr[hg19] 1q21.1q21.2(146,003,044_147,393,549)x3, 1q21.1(144,938,984_145,986,083)x1	1q21.1 Microduplication syndrome	#612475	Dup 1,391 kbp Del 1,047 kbp		Dup 18 Del 27		DD/ID, corpus callosum hypoplasia		N.D
66A	2/F	arr[hg19] 22q13.31q13.33(47,195,273_51,197,838)x1	Phelan-McDermid syndrome	#606232	Del 4,003 kbp	*SHANK3*	51		DD/ID, microcephaly,		N.D

Table 1 (continued)

Case	Age/ Sex	Region	Known syndrome	OMIM numbers	Type/Size	Critical genes or region	OMIM genes	Karyotype	Major clinical findings	Facial dysmorphology	Inheritance
67A	1/M	arr[hg19] 15q11 .2q13.1(22,770,421_28,660,038)x1	Prader-Willi/ Angelman syndrome	#105830	Del 5,890 kbp						N.D
68A	9/F	arr[hg19] 11q13.2(66,402,332_67,423,346)x1	Spinoserebeller Ataxi 5	#600224	Del 1,021kbp	*SPTBN2*(#604985)	42		ID, severe DD, hypotonia		N.D
69A	10/M	arr[hg19] Xq28(153,223,935_153,368,575)x2	Xq28 (MECP2) Duplication syndrome	# 300815	Dup 145kbp	*MECP2*	8		DD, epilepsy		N.D
70A	11/K	arr[hg19]2q33.1(197717566_197873563)x1	2q33.1 Microdeletion syndrome		Del 156 kbp		2		Short stature		N.D
71A	12/M	arr[hg19]18p11. 32q11.1(136227_18521285)x4	Tetrasomi 18p	#614290	Dup 18,385 kbp		73		DD/ID		N.D
72A	1/E	arr[GRCh37] 16p13.11(15531295_16391910)x1	16p13.11 Microdeletion syndrome		Del 861 kbp		10				N.D
73A	1/F	arr[GRCh37] 16p13.3p13.13(6597421_11821708) x1	16p13.2 Microdeletion syndrome	#616863	Del 5224 kbp	*USP7*	36		Hypotonia		N.D
74A	12/M	arr[GRCh37] 6q27(169810854_170919482)x1	6q27 Terminal Deletion syndrome		Del 1,109 kbp		343		DD/ID, epilepsy, cerebral palsy hydrocephaly		N.D
75A	20/F	arr[GRCh37] 17q12(34477480_36283612)x1	17q12 Deletion syndrome	#614527	Del 1,806 kbp		29		Premature ovarian insufficiency		N.D
76A	10/F	arr[GRCh37] 5p15.33(113577_676768) x1	Cri du chat syndrome	#123450	Del 563 kbp		17		DD, epilepsy		N.D
77A	2/F	arr[hg19] 17q21.31(43537167_44212310)x1	Koolen-de vries syndrome	#610443	Del 675 kbp	*KANSL1*	15		Microcephaly, epilepsy, bicuspid aorta	Strabismus	N.D

CMRI cranial magnetic resonance imaging, *VSD* ventricular septal defect, *DD* developmental delay, *PS* pulmonary stenosis, *ID* intellectual disability, *ASD* atrial septal defect, *MVP* mitral valve prolapse, *PDA* patent ductus arteriosus, *VUR* vesicoureteral reflux

[a]N.D.- not determined, because parents were not available for analysis

duplication syndrome (patient 62), and Mosaic trisomy 8 (Warkany syndrome 2) (patient 64) (Table 1).

Among the patients diagnosed according to the major clinical findings, 28 had DD/ID, 16 had DD, 9 had epilepsy, 8 had hypotonia, 4 had microcephaly, 3 had corpus callosum hypoplasia, 5 had autism, short stature 4, 12 in cardiovascular anomalies, and 11% of patients with other minor findings (Fig. 1).

In this cohort, 111 patients were positive through CMAs but their karyotype analyses results were negative. These findings highlight the importance of CMA analysis in cytogenetic analysis.

Discussion

In 2010, according to the American College of Medical Genetics (ACMG) practice guidelines, CMA testing for CNVs was recommended as a first-line test in the clinical genetic evaluation of unexplained DD/ ID [6]. Since then, CMA has been the first-tier test for patients presenting with DD/ID, ASD, and MCAHowever, another consensus statement was published in 2019 recommended whole exome sequencing as a first-tier test for patients with neurodevelopmental disorders [1].

In the present study, we conducted CMA analysis in 1277 patients with DD/ID, ASD, and MCA. To our knowledge, this study has the highest number of Turkish patients in reports of CMA ever published. The diagnostic rate of chromosomal abnormalities was 11 which is consistent with the results of previous studies 5–20% [7, 14]. Among the 135 patients diagnosed in this study, many patients have additional features that may contribute to the literature.

In previous studies conducted in the Turkish population, CNV rates ranged between 8.5 and 18.55% [15–18]. Ceylan et al. (2018) reported that of a group of 124 Turkish patients with intellectual disability and global developmental delay, 18.55% had pathogenic and likely pathogenic CNVs detected [15]. A study conducted by Ozyilmaz et al. (2016) reported that 13.6% of a group of 971 Turkish patients with developmental disabilities and congenital anomalies had pathogenic CNVs detected [16]. Özaslan et al. (2021) reported that 8.5% had pathogenic CNVs detected in a group of 47 Turkish patients with ASD [17]. In their study, Türkyılmaz et al. (2021) reported that 17.1% had pathogenic and likely pathogenic CNVs detected in a group of 139 Turkish patients with DD/ID [18]. Pathogenic and likely pathogenic CNVs have been evaluated in several studies. Our study results revealed that 11% of the study cohort showed all clinically relevant CNVs. The differences in CNV rates between the conducted studies, including ours, may be attributed to variations in sample sizes or the effect of VUS variants.

The major clinical findings showed that DD/ID has the highest diagnostic rate (77), followed by DD (16), epilepsy (9), hypotonia (8%), and microcephaly (%4). The diagnostic rates of other findings are shown in Fig. 1. Additional minor findings with very poor diagnostic values, according to radilogical findings, are endocrine disorders, hydrocephaly, behavioral problems, aggressiveness, and minor congenital anomalies such as cleft palate, cryptorchidism, and vesicoureteral reflux. Based on these findings, MCA should be the first step while selecting the test for diagnosing patients with DD/ID.

Patient 1B with phenotype-associated pathogenic CNV, shown in Table 2, presented with intellectual disability, learning disability, mitral valve prolapse (MVP), and bicuspite aortic valve. Microarray analysis revealed a 3,965 kbp deletion at 15q21.3q22.2 including the *TCF12* gene. Additionally, craniosynostosis-3 (CRS3)(OMIM #615,314) is caused by heterozygous mutation in the *TCF12* (OMIM #600,480) on chromosome 15q21. Pathogenic variants in *TCF12* were reported in patients with significant developmental delay or learning disability. Moreover, few reports documented chromosomal deletions including *TCF12* in patients with craniosynostosis and intellectual disability [19, 20]. *TCF12* heterozygous loss-of-function mutations have been associated with craniosynocytosis. Recently, intragenic deletions and duplications have been reported in 5 cases with TCF-related craniosynostosis and intellectual disability [21, 22]. To date, whole *TCF12* deletion has been reported in three patients. Firstly, coronal craniosynostosis and intellectual disability were reported in a patient with a deletion in the 15q21.3q22.2 region, including the *TCF12*, but a small duplication in the 2q21 region was accompanied as a result of maternal complex chromosomal rearrangement [20]. Second *TCF12* deletion was reported in a patient with developmental delay, dysmorphic features, seizures, and atrial septal defect [23]. Two of the four patients with *TCF12* deletion had atrial septal defects. Interestingly, MVP and bicuspid aortic valve were reported for the first time in our case. Accordingly, further investigations are required to determine whether MVP and bicuspid aortic valve are related to the TCF12 gene.

Patient 2B with phenotype-associated pathogenic CNV, shown in Table 2, a 12-year-old male, presented with intellectual disability, developmental delay, speech delay, learning disability, gait ataxia, and cerebellar cyst. Microarray analysis revealed a de novo genomic rearrangement including a 5,575 kbp deletion at 12p13.33p13.31 and a 3,057 kbp duplication at 17p13.3. Chromosome 12p deletions included *CACNA1C, ERC1, FBXL14, WNT5B, ADIPOR2, CACNA2D4, LRTM2,* and *DCP1B* that have been linked to the developmental verbal dyspraxia (DVD) and childhood apraxia of speech (CAS). Pathogenic variants of the *CACNA1C* gene are associated with autosomal dominant

Table 2 Patients with phenotype-associated pathogenic CNV

Case	Age/Sex	Region	Type/Size	Critical genes or region	OMIM genes	OMIM numbers	Karyotype	Major clinical findings
1B	9/M	arr[hg19] 15q21 .3q22.2(55,717,047–59,681,771)×1	Del 3,965 kbp	*TCF12*/ Pathogenic	31	#600,480	N	DD/ID, MVP, bicuspite aort
2B	12/M	arr[hg19] 12p13. 33p13.31(173,786–5,749,168)×1, 17p13.3(525–3,057,413)×3	Del 5,575 kbp Dup 3,057 kbp	Pathogenic/ Pathogenic De novo	Del 62 Dup 65		N	DD/ID
3B	0/F	arr[hg19] 7p22.3p11.1(43,360–58,006,205)×3	Dup 57,963 kbp	Pathogenic			46,XX, der(15)t(7;15)(p10;q10)	DD, fallot tetralogy, arachnodactyly, flexion contractures at the left wrist,
4B	16/F	arr[hg19] Xq23q28(110,130,760–155,233,731)×1	Del 45,103 kbp	*MECP2*/ Pathogenic		#300,005	46,X,del(X)(q23)	DD/ID, primary amenorrhea, hypoparathyroidism, ampliopia
5B	11/F	arr[hg19] 7q22 .3q31.2(105,182,994–115,880,277)×1	Del 10,697 kbp	*FOXP2*/ Pathogenic	49	#605,317	N	DD/ID
6B	6/M	arr[hg19] 3q23q26.2(141,752,803–167,921,496)×3, 4q22.1(89,756,392–91,083,051)×1	Dup 26,169 kbp Del 1,327 kbp	Pathogenic/ Uncertain			46 XY,t(3;16)	DD/ID, microcephaly,
7B	2/F	arr[hg19] 3p26.3p26.1(61,891–4,400,084)×1, 7q31 .2q36.3(115,563,546–159,119,707)×3	Del 4,338 kbp Dup 43,556 kbp	Uncertain/ Pathogenic			*	DD/ID, epilepsy
8B	2/F	arr[hg19] 7q34q36.3(141,627,148–159,119,707)×3, 9p24.3p24.2(203,861–4,557,165)×1	Dup 17,493 kbp Del 4,353 kbp	Pathogenic/ Pathogenic			46,XX,der(9)t(7;9)(q34;p24)	DD/ID
9B	2/M	arr[hg19] 7q33q36.3(137,878,650–159,119,707)×1	Del 21,241 kbp	Pathogenic De novo			46,XY,del(7)(q33)dn[29]/46,XY,dup(7)(q34q36)dn[21]	DD, hypotonia
10B	10/E	arr[hg19] 7q21. 11q21.13(81,477,235–89,747,380)×1, 1p31.3(67,889,570–68,618,237)×1	Del 8,270 kbp Del 729 kbp	Pathogenic/ Uncertain De novo			46,XY,t(1;4)(p?22;q?25),del(7)(q21.3)	DD/ID
11B	1/F	arr[hg19] Xp11 .4p11.3(41,359,369–45,761,138)×1	Del 4,402 kbp	Pathogenic	18		N	DD, hypotonia, microcephaly
12B	3/E	arr[hg19] 15q11 .2q13.2(22,770,421–30,329,208)×4	Dup 7,559 kbp	Pathogenic	139		47,XY,+idic(15)(15pter›	DD/ID, obesity
13B	2/F	arr[hg19] Xp22.31(6,897,848–8,233,972)×3	Dup 1,336kbp	Pathogenic	7		N	DD/ID, microcephaly, hypotonia, epilepsy, optical atrophy

Table 2 (continued)

Case	Age/Sex	Region	Type/Size	Critical genes or region	OMIM genes	OMIM numbers	Karyotype	Major clinical findings
14B	2/F	arr[hg19] 4q27q31.22(123,037,348–146,949,558)×1	Del 23,912kbp	Pathogenic			N	DD/ID, hypotonia, transposition of the great arteries
15B	6/F	arr[hg19] 6q14.1(78,962,580–82,945,456)×1	Del 3,983 kbp	Pathogenic	33			Mental retardation
16B	15/F	arr[hg19] 6p22.3(15321858_18203126)×1	Del 2,881 kbp	Pathogenic *ATXN1 and JARID2*	16	#601,556 #601,594		DD/ID, short stature
17B	15/M	arr[hg19] Xp22.31(6555280_8156174)×0	Del 1601 kbp	Pathogenic	5			ID, attention deficit hyperactivity disorder
18B	23/M	arr[hg19] 4q31.23q35.2(150125470_190957473)×3, 8p23.3p23.2(158048_4071351)×1	Dup 40,832 kbp Del 3,913 kbp	Pathogenic/ Pathogenic	207/ 21		46,XY,add(8)(p23)	DD/ID
19B	27/M	arr[hg19] 4q31.23q35.2(150125470_190957473)×3, 8p23.3p23.2(158048_4071351)×1	Dup 40,832 kbp Del 3,913 kbp	Pathogenic/ Pathogenic	207/ 21		46,XY,add(8)(p23)	DD/ID
20B	5/M	arr[hg19] 10p15.3p15.2(2059990_3154109)×3, 16p11.2(29580610_30226930)×1	Dup 1,094 kbp Del 646 kbp	Uncertain/ Pathogenic	3/ 35		46,Y,fra(X)(q27)[23]/46,XY[27]	DD/ID
21B	7/E	arr[hg19] 17q12(34461488_36433105)×3	Dup 1,972 kbp	Pathogenic	35			DD/ID
22B	3/M	arr[hg19] 19p13.2(8,751,106–12115579)×1	Del 3.364 kbp	Pathogenic	118		N	DD/ID, epilepsy, learning disability, speech delay
23B	11/F	arr[hg19]7q34q36.1(140,776,614–149472508)×1	Del 8,696 kbp	Pathogenic	97		46,XX,del(7)(q34q36)	Mental retardation, cerebral atrophy, epilepsy
24B	18/M	arr[GRCh37] 1q25.3q41(182712469_223434633)×3	Dup 40,722 kbp	Pathogenic	342			DD/ID, obesity
25B	4/F	arr[hg19] 3q13.2q13.33(111,991,197–119,483,267)×1	Del 7,492 kbp	*ZBTB20* Pathogenic	65	#606,025	N	ID

VSD ventricular septal defect, *ASD* atricular septal defect, *MVP* mitral valve prolapse, *DD* developmental delay, *ID* ıntellectual disability, *N* Normal

*As a result of subtelomeric FISH (fluorescent insitu hybridization) analysis, number 3 Monosomy related to the p ter region of chromosome 7 and trisomy related to the q ter region of chromosome 7

Table 3 Patients with CNV of uncertain clinical significance

Case	Age/Sex	Region	Type/Size	Critical genes or region	OMIM genes	Karyotype	Major clinical findings
1C	7/M	arr[hg19] 2p25.3(249,091_734,905)x3	Dup 486 kbp	*MYT1L*/ Uncertain	5	N	Autism, aggressiveness, self destructive behavior
2C	8/F	arr[hg19] 1q41(222,697,087_224,051,439)x3	Dup 1,354 kbp	Uncertain	14	N	Autism
3C	8/E	arr[hg19] 4q35.2(189,627,147_190,957,473)x1	Del 1,330 kbp	Uncertain	5	N	Autism
4C	17/M	arr[hg19] 17q12(31,955,152_32,947,102)x3	Dup 992 kbp	Uncertain	10	47XY+MAR	DD/ID, velopharyngeal insufficiency
5C	0/M	arr[hg19] Yp11.2(4,526,543_6,505,825) x0	Del 1,979 kbp	Uncertain	15	N	Autism, DD/ID, epilepsy
6C	7/M	arr[hg19] 13q14.11(43,524,100_44,450,346)x3	Dup 926 kbp	Uncertain	5	N	Autism
7C	3/M	arr[hg19] 2q32.3(193,602,929_194,490,513)x1	Del 888 kbp	*PCGEM1* /Uncertain		N	Autism
8C	0/E	arr[hg19] 11q21q23.3(94,425,766_116, 690,578)x1	Del 22,265 kbp	Uncertain		46,XY,del(11)(q14q23)	Neonatal hypotonia, right optic atrophy
9C	10/M	arr[hg19] 2p25.3(249,091_734,905)x3	Dup 486 kbp	Uncertain	5	N	Autism, aggressiveness
10C	7/M	arr[hg19] 14q32.33(105871768_107285437)x1	Del 1,414 kbp	Uncertain	21	N	Autism, aggressiveness
11C	10/E	arr(X)x1, (Y)x2				47,XYY	ID, epilepsy, short stature
12C	8/E	arr[hg19] Yq11.2 23q11.23(25,772,061_28,172,000)x2	Dup 2,400 kbp	Uncertain	19	47,XY,+8[15]/46,XY[35]	ID, short stature, GH deficiency
13C	16/F	arr[hg19] Xp11.23(48801983_49470545)x1	Del 669 kbp	Uncertain	39		Short stature
14C	1/M	arr[hg19] 11p11.2p11.12(48327185_49228613) x3	Dup 901 kbp	Uncertain	6		Hypotonia, macrocephaly, macrosomia
15C	13/F	arr[hg19] 10q25.2(112828393_114468137)x3	Dup 1,640 kbp	Uncertain	9		ID, obesity
16C	12/F	arr[hg19] 6q21q22.31(111623202_120485517) x3	Dup 8,862 kbp	Uncertain	56		DD/ID, neonatal hypotonia
17C	15/F	arr[hg19] 6q12(66289182_67430334)x3	Dup 1,141 kbp	Uncertain	2		Primary amenorrhea
18C	26/M	arr[hg19] 22q11.1q11.21(16888899_18153009) x4	Dup 1,264 kbp	Uncertain	18		Hypergonadotropic hypogonadism

Table 3 (continued)

Case	Age/Sex	Region	Type/Size	Critical genes or region	OMIM genes	Karyotype	Major clinical findings
19C	1/F	arr[hg19] 15q11.2(22770421_ 23654294)x3	Dup 884 kbp	Uncertain	11		DD
20C	7/M	arr[hg19] 6q25.3(155751813_156162006)x1	Del 410 kbp	Uncertain			ID
21C	2/M	arr[hg19] 13q31.1(79259453_81127249)x1	Del 1,868 kbp	Uncertain	10		DD/ID, short stature
22C	6/M	arr[hg19] 15q11.2(22,770,421_23,214,984)x3	Dup 445 kbp	Uncertain	6	N	ID, learning disability obesity
23C	3/M	arr[hg19] 4q31.3q32.1(154958319_156353245) x3, Yq11.2 21q11.222(19571466_21000961)x0	Dup 1,395 kbp Del 1,429 kbp	Uncertain/ Uncertain	8/ 10	N	DD/ID, hypotonia, microcephaly, epilepsy, ASD,VSD
24C	7/M	arr[hg19] 9p13.3(33334956_33893073) x1	Del 558 kbp	Uncertain	13	N	DD/ID, Autism
25C	9/M	arr[hg19] 2q21.3q22.1(136511816_136925439) x3, 19q13.2(38748912_39416409)x3	Dup 414 kbp Dup 667 kbp	Uncertain/ Uncertain	7/ 26	N	ID
26C	5/F	arr[hg19] 17q22q23.1(57185806_57700581)x3	Dup 515 kbp	Uncertain	11		DD/ID, aggressiveness
27C	15/F	arr[hg19] 3p26.3p26.2(61891_2949863) x3	Dup 2,888kbp	*CNTN6* *CLH1* Uncertain	7	N	Short stature
28C	17/F	arr[hg19] Xp22.33(562296_3008272)x3	Dup 2,446 kbp	Uncertain SHOX	25	N	DD/ID
29C	12/M	arr[hg19] Xp11.23(47693253_48283225)x2	Dup 590 kbp	Uncertain	13	N	ID, epilepsy
30C	6/M	arr[hg19] 15q11.2(22,770,421_23,214,984)x3	Dup 445 kbp	Uncertain	4		ID, obesity
31C	0/M	arr[hg19] 22q11. 22q11.23(22,962,961_25,059,631)x3	Dup 2,097 kbp	Uncertain	52	N	Polydactyly, macrocephaly, hydronephrosis, ASD
32C	2/M	arr[hg19] 10q11.22(46,293,590_48,164,458)x1	Del 1,871 kbp	Uncertain	23	N	Cerebral palsy, epilepsy
33C	5/M	arr[hg19] Xq13.1(70356641_70510791) x2	Dup 154 kbp	Uncertain	6		DD

VSD ventricular septal defect, *ASD* atriel septal defect, *MVP* mitral valve prolapse, *DD* developmental delay, *ID* intellectual disability, *N* Normal

inheritance, "Neurodevelopmental disorder with hypotonia, language delay, and skeletal defects with or without seizures" (OMIM #620,029). 12p13.33 deletion has been associated to mild intellectual disability, speech delay, and motor skills impairment [24, 25]. Chromosome 17p13.3 duplication syndrome (OMIM #613,215) is characterized by developmental delay, autism, abnormal growth, facial dysmorphism, and structural brain abnormalities [26, 27]. This duplication on the 17p13.3 region, involves *PAFAH1B1, YWHAE,* and *CRK* genes. According to Bruno et al., class II duplication encompasses *PAFAH1B1* and may also include *CRK* and *YWHAE*. Bruno DL et al. suggested class

Table 4 The number and percentage of patients diagnosed with single well-known genetic syndrome

Syndrome name	OMIM #	Number of cases	Number of cases % of total cases(1227)	Number % of total solved cases(135)
1q21.1 Microduplication syndrome	612,475	2	0.16	1.48
1q21.1 Deletion syndrome	612,474	1	0.08	0.74
1p36 Deletion syndrome	607,872	1	0.08	0.74
2q33.1 Microdeletion syndrome		1	0.08	0.74
Glucogen storage disease type-4	232,500	1	0.08	0.74
Wolf-hirschhorn syndrome	194,190	3	0.24	2.22
Cri du chat syndrome	123,450	1	0.08	0.74
Bosch-boonstra-schaaf optic atrophy syndrome	615,722	1	0.08	0.74
6q27 Terminal deletion syndrome		2	0.16	1.48
Joubert syndrome	614,464	1	0.08	0.74
Williams-beuren syndrome	194,050	3	0.24	2.22
7q11.23 Duplication syndrome	609,757	1	0.08	0.74
Monosomy in distal 8p syndrome		1	0.08	0.74
Mosaic trisomy 8(warkany syndrome 2)		1	0.08	0.74
Nicolaides–baraitser syndrome	601,358	1	0.08	0.74
9p Duplication syndrome		1	0.08	0.74
Kleefstra syndrome	610,253	2	0.16	1.48
10q22.3-q23.2 Deletion syndrome	612,242	1	0.08	0.74
10p15.3 Microdeletion syndrome		1	0.08	0.74
Spinoserebeller ataxi 5	600,224	1	0.08	0.74
Coffın-siris syndrome 6	617,808	1	0.08	0.74
Impaıred intellectual development and distinctive facial features with or without cardiac defects; MRFACD	616,789	1	0.08	0.74
15q11 Tetrasomy syndrome		1	0.08	0.74
Prader-willi/angelman syndrome	105,830	4	0.32	2.96
15q24 Microdeletion syndrome	613,406	1	0.08	0.74
15q13.3 Microdeletion syndrome	612,001	2	0.16	1.48
Ayme-gripp syndrome	601,088	1	0.08	0.74
16q12 Microdeletion syndrome	-	1	0.08	0.74
16p11.2 Microdeletion syndrome	611,913	1	0.08	0.74
16p13.11 Microdeletion syndrome		3	0.24	2.22
16p13.2 Microdeletion syndrome	616,863	1	0.08	0.74
16p13.11 Microduplication	-	3	0.24	2.22
Potocki-lupski syndrome	610,883	1	0.08	0.74
Miller dieker syndrome	247,200	1	0.08	0.74
Koolen-de vries sendromu	610,443	1	0.08	0.74
17q12 deletion syndrome	614,527	1	0.08	0.74
Smith magenis syndrome	182,290	2	0.16	1.48
18p Monosomy syndrome	-	1	0.08	0.74
Tetrazomi 18p syndrome	614,290	1	0.08	0.74
18q Deletion syndrome	601,808	1	0.08	0.74
18q23 Deletion syndrome	-	1	0.08	0.74
Phelan-McDermid syndrome	606,232	2	0.16	1.48
22q11.2 Microduplication syndrome	608,363	1	0.08	0.74
22q11.2 Microdeletion syndrome	611,867	4	0.32	2.96
Xq28 Mikroduplication syndrome	300,815	2	0.16	1.48
Pelizaeus-merzbacher syndrome	312,080	2	0.16	1.48
Klinefelter syndrome	-	1	0.08	0.74
Duchanne muscular dystrophy	310,200	2	0.16	1.48

Table 4 (continued)

Syndrome name	OMIM #	Number of cases	Number of cases % of total cases(1227)	Number % of total solved cases(135)
Leri weill diskondrosteozis(LWD)	127,300	1	0.08	0.74

Table 5 The number and percentage of patients diagnosed with multiple well-known genetic syndrome

Syndrome name	OMIM #	Number of cases	Number of cases % of total cases(1227)	Number % of total solved cases(135)
Primrose syndrome/turner syndrome	259,050	1	0,08	0,74
12p13.33 Deletion syndrome/ 17p13.3 duplication syndrome	-/613215	1	0,08	0,74
Down syndrome/CMT syndrome	190,685/118220	1	0,08	0,74

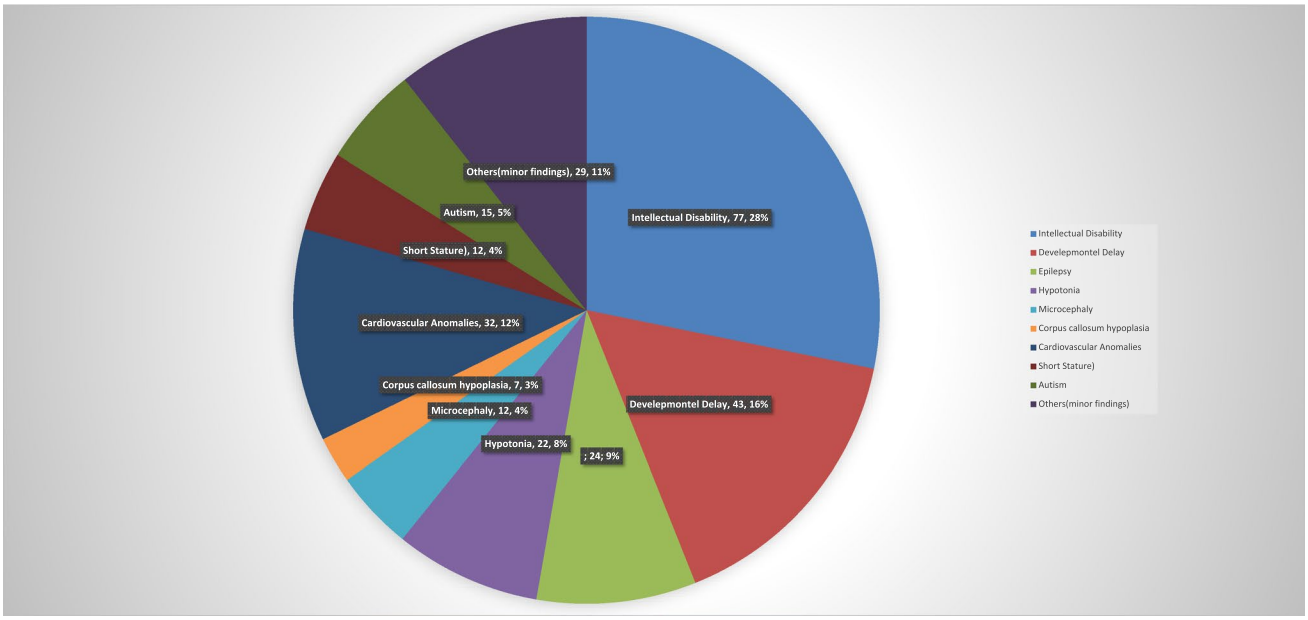

Fig. 1 Diagnosis rates according to major clinical findings

I duplication includes the *YWHAE* gene, but not specifically PAFAH1B1. However, class II duplication always contained *PAFAH1B1, CRK, and YWHAE* genes. Class II microduplications are characterized by moderate to mild developmental and psychomotor delay and hypotonia. The patient had similar features with class II microduplication. Patient 5 who had a combined 17p duplication and 12p deletion had a normal constitutional karyotype, and his parents' karyotypes were also normal. Besides, his parents' CMAs were normal. However, in the FISH analysis of the parents, it was determined that this complex change occurred as a result of abnormal segregation of the balanced translocation in the father.

As seen in this case, we were able to detect parents with balanced chromosome carriers by applying both chromosome analysis and the FISH method. Accordingly, chromosome analysis and FISH should be performed to determine the balanced chromosome carriers.

Patient 3B with phenotype-associated pathogenic CNV, presented with developmental delay, fallot tetralogy, arachnodactyly, and flexion contractures at the left wrist (Table 2). G-banded karyotype analysis revealed 46,XX,der(15)t(7;15)(p10;q10)pat. Microarray analysis revealed a 57,963 kbp duplication at 7p22.3p11.1. Recently, several cases of 7p duplications have been reported. However, various cardiac anomalies have been reported in 6 of 18 patients with chromosome 7p duplication, this is the first patient that the tetralogy of Fallot reported [28]. Deletions of chromosome 7p may be accompanied by tetralogy of Fallot in 4 patients [29].

Patient 29A with a well-known genetic syndrome, shown in Table 1, a 2-year-old girl who presented with hypotonia. She was unable to sit, walk or talk. Physical examination

revealed intellectual disability, developmental delay, microcephaly, scaphocephaly, sparse hair, clinodactyly, and reduced hand subcutaneous fat. Both brain magnetic resonance imaging and echocardiography were within normal limits. A conventional cytogenetic study revealed 46,XX,add(15)(p11.2). Parental chromosomes were normal. Microarray analysis revealed a 38,584 kbp de novo duplication at 9p24.3p13.1. *SMARCA2* gene is associated with Nicolaides–Baraitser syndrome (NCBRS; OMIM#601,358) and Coffin-Siris syndrome (CSS; OMIM#135,900) but *SMARCA2* mutations causing NCBRS are likely to act through a dominant-negative effect [30].

Patient 43A with a well-known genetic syndrome shown in Table 1, a 19-year-old male patient who presented with intellectual disability and developmental delay. He had learning disability, epilepsy, congenital cataract, scoliosis, and growth hormone deficiency. Additionally, he had a broad nasal root and arachnodactyly. Microarray analysis revealed a 4,350 kbp deletion at 16q23.1q23.3. According to Javadiyan et al. (2017) and Alkhunaizi et al. (2019), *MAF* gene heterozygote variations are associated with Aymé-Gripp syndrome [31, 32]. It is the first time to report a case with heterozygous deletions of chromosome 16q23 encompassing the *MAF* gene. The patient's 48-year-old father and aunt had undergone cataract surgery. The couple is nonconsanguineous, also the mother is healthy.

Also, the karyotype and microarray results of the parents of cases 9B, 10B, 11B, and 14B from Table 2 as well as cases 4C and 29C from Table 3 were found to be normal. These results support the pathogenicity of the variations detected in patients. However, as one of the limitations of our study, we could not perform karyotype and microarray analysis on the mothers and fathers of patients in Tables 2 and 3.

Conclusion

As a result, CMA may be beneficial in identifying microdeletions and microduplications, and has played an important role in the diagnosis and genetic counseling of patients. Here in, we present an analysis of patients with deletions and duplications, as well as novel and previously unreported findings. The study's findings highlight the importance of CMA analysis in cytogenic examinations since patients exhibited positive results on the CMA test but negative results with karyotype analyses. This article presents multiple cases with new findings. In order to contribute to the literature, some patients are explained in detail above.

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Declarations

Competing interests The authors declare no competing interests.

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References

1. Stankiewicz P, Beaudet AL (2007) Use of array CGH in the evaluation of dysmorphology, malformations, developmental delay, and idiopathic mental retardation. Curr Opin Genet Dev 17(3):182–192
2. Anagnostou E, Zwaigenbaum L, Szatmari P et al (2014) Autism spectrum disorder: advances in evidence-based practice. CMAJ 186:509–519. https://doi.org/10.1503/cmaj.121756
3. Khan NZ, Gallo LA, Arghir A et al (2012) Autism and the grand challenges in global mental health. Autism Res 5:56–59. https://doi.org/10.1002/aur.1239
4. Shen Y, Dies KA, Holm IA et al (2010) Clinical genetic testing for patients with autism spectrum disorders. Pediatrics 125(4):727–735. https://doi.org/10.1542/peds.2009-1684
5. Waye MMY, Cheng HY (2018) Genetics and epigenetics of autism: a review. Psychiatry Clin Neurosci 72:228–244. https://doi.org/10.1111/pcn.12606
6. Manning M, Hudgins L (2020) Array-based technology and recommendations for utilization in medical genetics practice for detection of chromosomal abnormalities. Genet Med 22:2126. https://doi.org/10.1038/s41436-020-0847-9
7. Miller DT, Adam MP, Aradhya S et al (2010) Consensus statement: chromosomal microarray is a first-tier clinical diagnostic test for individuals with developmental disabilities or congenital anomalies. Am J Hum Genet 86:749–764. https://doi.org/10.1016/j.ajhg.2010.04.006
8. Riggs ER, Wain KE, Riethmaier D et al (2014) Chromosomal microarray impacts clinical management. Clin Genet 85:147–153. https://doi.org/10.1111/cge.12107
9. Maulik PK, Mascarenhas MN, Mathers CD, Dua T, Saxena S (2011) Prevalence of intellectual disability: a meta-analysis of population-based studies. Res Devel Disabil 32:419–436. https://doi.org/10.1016/j.ridd.2010.12.018
10. Bartnik M, Nowakowska B, Derwińska K, Wiśniowiecka-Kowalnik B, Kędzior M, Bernaciak J et al (2014) Application of array comparative genomic hybridization in 256 patients with developmental delay or intellectual disability. J Appl Genet 55:125–144. https://doi.org/10.1007/s13353-013-0181-x
11. Battaglia A, Doccini V, Bernardini L et al (2013) Confirmation of chromosomal microarray as a first-tier clinical diagnostic test for individuals with developmental delay, intellectual disability,

autism spectrum disorders and dysmorphic features. Eur J Paediatr Neurol 17:589–599. https://doi.org/10.1016/j.ejpn.2013.04.010
12. Zarrei M, Burton CL, Engchuan W et al (2019) A large data resource of genomic copy number variation across neurodevelopmental disorders. NPJ Genom Med 7:26. https://doi.org/10.1038/s41525-019-0098-3
13. Sagoo GS, Butterworth AS, Sanderson S, Shaw-Smith C, Higgins JP, Burton H (2009) Array CGH in patients with learning disability (mental retardation) and congenital anomalies: updated systematic review and meta-analysis of 19 studies and 13,926 subjects. Genet Med 11:139–146. https://doi.org/10.1097/GIM.0b013e318194ee8f
14. Riggs ER, Andersen EF, Cherry AM et al (2020) Technical standards for the interpretation and reporting of constitutional copy number variants: a joint consensus recommendation of the american college of medical genetics and genomics (ACMG) and the clinical genome resource (ClinGen). Genet Med 22:245–257. https://doi.org/10.1038/s41436-019-0686-8
15. Ceylan AC, Citli S, Erdem HB et al (2018) Importance and usage of chromosomal microarray analysis in diagnosing intellectual disability, global developmental delay, and autism; and discovering new loci for these disorders. Mol Cytogenet 11:54. https://doi.org/10.1186/s13039-018-0402-4
16. Ozyilmaz B, Kirbiyik O, Koc A et al (2016) Experiences in microarray-based evaluation of developmental disabilities and congenital anomalies. Clin Genet 92:372–379. https://doi.org/10.1111/cge.12978
17. Özaslan A, Kayhan G, İşeri E et al (2021) Identification of copy number variants in children and adolescents with autism spectrum disorder: a study from turkey. Mol Biol Rep 48:7371–7378. https://doi.org/10.1007/s11033-021-06745-8
18. Türkyılmaz A, Geckinli BB, Tekin E et al (2022) Array-based comparatıve genomıc hybrıdızatıon analysıs ın chıldren wıth developmental delay/ıntellectual dısabılıty. Balkan Journal of Medical Genetics 24:15–24
19. Hiraki Y, Moriuchi M, Okamoto N, Ishikawa N, Sugimoto Y, Equchi K et al (2008) Craniosynostosis in a patient with a de novo 15q15-q22 deletion. Am J Med Genet 146:1462–1465. https://doi.org/10.1002/ajmg.a.32339
20. Tanno PL, Poreau B, Devillard F et al (2014) Maternal complex chromosomal rearrangement leads to TCF12 microdeletion in a patient presenting with coronal craniosynostosis and intellectual disability. Am J Med Genet 164A:1530–1536. https://doi.org/10.1002/ajmg.a.36467
21. Piard J, Rozé V, Czorny A et al (2015) TCF12 microdeletion in a 72-year-old woman with intellectual disability. Am J Med Genet 167A:1897–1901. https://doi.org/10.1002/ajmg.a.37083
22. Goos JAC, Fenwick AL, Swagemakers SMA et al (2016) Identification of intragenic exon deletions and duplication of TCF12 by whole genome or targeted sequencing as a cause of TCF12-related craniosynostosis. Hum Mutat 37:732–736. https://doi.org/10.1002/humu.23010
23. Yoon JG, Hahn HM, Choi S et al (2020) Molecular diagnosis of craniosynostosis using targeted next-generation sequencing. Neurosurgery 87:294–302. https://doi.org/10.1093/neuros/nyz470
24. Fanizza I, Bertuzzo S, Beri S et al (2014) Genotype phenotype relationship in a child with 2.3 Mb de novo interstitial 12p13.33-p13.32 deletion. Eur J Med Genet 57:334–338. https://doi.org/10.1016/j.ejmg.2014.04.009
25. Thevenon J, Callier P, Andrieux J et al (2013) 12p13.33 microdeletion including ELKS/ERC1, a new locus associated with childhood apraxia of speech. Eur J Med Genet 21:82–88. https://doi.org/10.1038/ejhg.2012.116
26. Chloe SA, Francis D, McGillivray G, Lockhart PL, Leventer RJ (2019) Polymicrogyria associated with 17p13.3p13.2 duplication: case report and review of the literatüre. Eur J Med Genet 63:103774. https://doi.org/10.1016/j.ejmg.2019.103774
27. Curry CJ, Rosenfeld JA, Grant E et al (2013) The duplication 17p13.3 phenotype: analysis of 21 families delineates developmental, behavioral and brain abnormalities, and rare variant phenotypes. Eur J Med Genet 161:1833–1852. https://doi.org/10.1002/ajmg.a.35996
28. Chui JV, Weisfeld-Adams JD, Tepperberg J, Mehta L (2011) Clinical and molecular characterization of chromosome 7p22.1 microduplication detected by array CGH. Am J Med Genet 155:2508–2511. https://doi.org/10.1002/ajmg.a.34180
29. Schmidt B, Cate FU, Weiss M, Koehler U (2012) Cardiac malformation of partial trisomy 7p/monosomy 18p and partial trisomy 18p/monosomy 7p in siblings as a result of reciprocal unbalanced malsegregation–and review of the literatüre. Eur J Pediatr 171:1047–1053. https://doi.org/10.1007/s00431-012-1682-z
30. Sousa SB, Hennekam RC (2014) Phenotype and genotype in nicolaides-baraitser syndrome. Am J Med Genet 166:302–314. https://doi.org/10.1002/ajmg.c.31409
31. Javadiyan S, Craig JE, Sharma S et al (2017) Novel missense mutation in the bZIP transcription factor, MAF, associated with congenital cataract, developmental delay, seizures and hearing loss (Aymé-Gripp syndrome). BMC Med Genet 18:52. https://doi.org/10.1186/s12881-017-0414-7
32. Alkhunaizi E, Koenekoop RK, Saint-Martin C, Russell L (2019) Maternally inherited MAF variant associated with variable expression of aymé-Gripp syndrome. Am J Med Genet 179:2233–2236. https://doi.org/10.1002/ajmg.a.61299