# Clinical characteristics of children with neurodevelopmental delay and pathogenic copy number variations who underwent microarray analysis

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## INTRODUCTİON

Global developmental delay (GDD), intellectual disability (ID), and autism spectrum disorders (ASD) are neuro-developmental disorders that are frequently seen in pediatric neurology practice. Genetic or chromosomal disorders are the most common etiology in patients presenting with neuro-developmental disorders. If a specific diagnosis cannot be made after systemic clinical evaluation, chromosomal microarray (CMA) is the first-line test with the highest diagnostic value. CMA can detect copy number variations (CNV) smaller than 1Mb. Pathogenic CNV was found on average 7.8% in patients with developmental delays and 10.6% in children with syndromic features (1)

## OBJECTIVES

In this study we aimed to define the clinical characteristics of children with neurodevelopmental delay and pathogenic copy number variations (CNV) in chromosomal microarray. Pathogenicity of CNVs were identified according to Miller et al. (2), and American College of Medical Genetics guidelines (3). Segregation analysis could not be performed on all patients due to loss of follow-up, lack of family consent or financial reasons.

## MATERIALS&METHODS

Children aged 0-18 years, who were evaluated for neurodevelopmental delay, from August 2017 to March 2021, in pediatric genetics and pediatric neurology outpatient clinic at a tertiary hospital, and had pathogenic CNVs were retrospectively analyzed.

## RESULTS

Twenty-six children were included, 15 (57.7%) of them were girls. Mean age at diagnosis was 47.640.5 months (age range: 4-133 months) (Table 1). Most of the children (n=19, 73%) were diagnosed with well defined OMIM microdeletion/microduplication syndromes (table 2). Of CNV's 21 (80.8%) were deletions, 5 (19.2%) were duplications. Fifteen (57.7%) of them had GDD, 7 (31.8%) had ID and 5 (19.2%) had ASD. History of a preterm birth and birth weight small for gestational age were present in 4 and 5 children respectively. Neuroimaging was compatible with hypoxic ischemic injury in 2 children (patient 8 and 13) and hypoglycemic sequel in 1 patient (patient 17). One patient with mosaic tetrasomy 12p (patient 21), had a large deletion (11 Mb), prenatal genetic tests on chorionic villus samples, including karyotype and CMA analysis (with a lower resolution) and whole exome sequence analysis were found to be normal.

Facial dysmorphism was present in 20 (76.9%), hypotonicity in 14 (53.8%), epilepsy in 9 (34.6%), microcephaly in 7 (26.9%), macrocepahly in 2 (7.7%), hearing impairment in 2 (7.7%), visual impairment in 3 (11.5%) children.

**Table 1: Clinical findings of children with pathogenic copy number variations**

| Clinical findings | Frequency/total number of patients evaluated (%) |
|---|---|
| History of preterm birth | 4/26 (15.4) |
| Birth weight | |
| AGA | 20/26 (76.9) |
| SGA | 5/26 (19.2) |
| LGA | 1/26 (3.8) |
| Parental consanguinity | 8/26 (30.8) |
| Positive first degree family history | 3/26 (11.5) |
| Global developmental delay | 15/26 (57.7) |
| Mild | 8 |
| Moderate to severe | 7 |
| Intellectual disability | 7 (26.9) |
| Mild | 5 |
| Moderate to severe | 2 |
| Autism spectrum disorder | 5 (19.2) |
| Head circumference | |
| Microcephaly | 7/26 (26.9) |
| Macrocephaly | 2/26 (7.7) |
| Tonus | |
| Hypotonicity | 14/26 (53.8) |
| Hypertonicity | 2/26 (7.7) |
| Facial dysmorphism | 20/26 (76.9) |
| Hearing impairment | 2/26 (7.7) |
| Visual impairment | 3/26 (11.5) |
| Epilepsy (seizure control is defined in 8 patients) | 9/26 (34.6) |
| Seizure control with monotherapy | 6/8 |
| Seizure control with two anti-seizure drugs | 1/8 |
| Drug-resistant epilepsy | 1/8 |
| EEG findings | 6/14 (42.9) |
| Focal anomaly | 3 |
| Generalized anomaly | 3 |
| Abnormal cranial MRI | 6/20 (30) |
| Accompanying major anomaly | 6/20 (30) |

## CONCLUSIONS

Chromosomal microarray analysis is a useful tool in patients with unexplained neurodevelopmental delay. Even in children with brain injury secondary to perinatal asphyxia and neonatal hypoglycemia, microarray analysis should be requested in cases of concomitant dysmorphism and/or multisystem involvement. Enabling an accurate etiologic diagnosis in patients with neurodevelopmental delay is important for better clinical management, follow-up for possible complications, genetic counselling after segregation analysis for sub-sequent pregnancies and avoiding unnecessary tests.

**Table 2: Summary of phenotype and cytogenetic data of patients**

| Patient no/ gender/age | Clinical features | Copy number variations | Size | Inheritance | Associated gene or chromosome locus, references |
|---|---|---|---|---|---|
| 1/F/8y5m | Mild ID, epilepsy, preterm SGA | arr 3q27.1q29(184,326,528-192,863,237)x1 | 8.5 Mb | unknown | DECIPHER: 292123, 275722, 276534, 281790 |
| 2/M/5y5m | ASD, epilepsy, dysmorphism | arr 16p12.2(21,601,714-21,963,662)x1 | 362 Kb | unknown | Chromosome 16p12.2-p11.2 deletion syndrome (OMIM# 613604) |
| 3/F/10y8m | ASD, mild ID | arr 7p22.3(1,132,971-2,348,853)x1 | 1.2 Mb | unknown | ISCA: nssv14082213 |
| 4/F/2y8m | ASD, macrocephaly | arr7p22.2p22.1(4,186,277-6,601,751)x3 | 2.4 Mb | de novo | 7p22.1 duplication syndrome (PMID: 27866048) (14) |
| 5/M/10y8m | Epilepsy, mild ID, macrocephaly | arr22q11.21(20,716,876-21,927,646)x1 | 1.2 MB | unknown | 22q11.2 deletion syndrome (DiGeorge syndrome) (OMIM# 188400) |
| 6/M/7y4m | Severe ID, hypotonia, dysmorphism, corpus callosum dysgenesis, hirsutism, feeding problems | arr6q25.3(155,751,813-157,398,175)x1 | 1.6 Mb | unknown | ARID1B gene, Coffin Siris syndrome (OMIM# 135900) |
| 7/F/9m | GDD, hypotonia, dysmorphism, hypomyelination, corpus callosum dysgenesis | arr4q34.1(173,854,451-175,026,757)x1 | 1.2 Mb | de novo | DECIPHER: 267783 ISCA: nssv578000 |
| 8/F/6m | GDD, dysmorphism, preterm SGA, hearing loss, microcephaly, hypertonia, periventricular leukomalacia | arr18p11.32p11.21(136,226-14,978,127) x4 | 14.8 Mb | de novo | Tetrasomy 18 p, isochromosome 18p syndrome (OMIM# 614290) |
| 9/F/13m | GDD, hypotonia, dysmorphism, | arr18q12.2q21.1(34,504,506-46,532,088)X1 | 12 Mb | de novo | Chromosome 18q deletion syndrome (OMIM# 601808) |
| 10/F/3y11m | GDD, hypotonia, term SGA, bilateral anophtalmia, dysmorphism, extremity anomalies | 1-arr3p26.3(61,891-2,070,846) x1<br>2-arr4q35.1q35.2(185,721,369-190,957,473) x1<br>3-arr13q31.13q34(92,732,335-115,107,733)x3* | 1-2 Mb<br>2-5.2 Mb<br>3-22.4Mb | 1-paternal (2Mb)<br>2-de novo<br>3- de novo | 3*PMID: 25337073 (15) |
| 11/M/4m | GDD, preterm SGA, hypertonicity, microcephaly, duplicated collecting system in kidneys | 1. arr21q22(45,973,877-48,097,372)x3<br>2. arr22q13.2q13.33 (42,592,238-51,197,838)x1* | 1-2 Mb<br>2- 8.6 Mb | unknown | 2*Chromosome 22q13.3 deletion syndrome (Phelan McDermid syndrome) (OMIM# 606232) |
| 12/F/ 11y1m | mild ID, dysmorphism, sensorineural hearing loss | arr22q11.21(20,742,449-21,804,886)x3 | 1.1 Mb | unknown | Chromosome 22q11.2 microduplication syndrome (OMIM# 608363) |
| 13/F/2y1m | GDD, hypotonia, microcephaly, epilepsy, dysmorphism, tracheostomised, cardiomyopathy, strabismus, periventricular leukomalacia | arr1p36.33p.36.32(849,466-5,021,200)<br>46,XX,del(1)(p36.3) | 4.2Mb | de novo | 1p36 del syndrome (OMIM# 607872) |
| 14/M/20m | GDD, hypotoni, microcephaly, dysmorphism | arr15q11.2q13.1(23,291,158-28,828,168)X1 | 5.5Mb | unknown | Angelman syndrome (OMIM# 105830) |
| 15/F/9 m | GDD, hypotonia, dysmorphism, hyperpigmentation along Blaschko's lines, opticatrophy | arr12p13.33p11.22(191619-28756107)x2-4 | 28.5Mb | unknown | Mosaic tetrasomy 12p syndrome (Pallister-Killian syndrome) (OMIM# 601803) |
| 16/M/2y4m | GDD, hypotonia, term LGA | arr15q13.2q13.3(31,073,668-32,914,239)x1 | 1.8 Mb | de novo | 15q13.3 deletion syndrome (OMIM# 612001) |
| 17/M/6y10m | Severe ID, refractory epilepsy, hypotonia, microcephaly, visual impairment, dysmorphism. Clinical findings and MRI are compatible with neonatal hypoglycemic sequel | arr1p36.33(849,466-1,992,748)x1 | 1.1 Mb | de novo | 1p36 deletion syndrome (OMIM# 607872) |
| 18/M/7m | GDD, hypotonia, dysmorphism | arr16p11.2(29,567,295-30,226,593)x1 | 660Kb | unknown | Chromosome 16p11.2 deletion syndrome 593 Kb (OMIM# 611913) |
| 19/M/4y | GDD, epilepsy | arr16p11.2(29634212_30199805)x1 | 566Kb | de novo | Chromosome 16p11.2 deletion syndrome593 Kb (OMIM# 611913) |
| 20/F/14m | GDD, epilepsy, hypotonia | arr16p11.2(29634212-30199805)x1 | 565Kb | unknown | Chromosome 16p11.2 deletion syndrome593 Kb (OMIM# 611913) |
| 21/F/13m | GDD, microcephaly, hypotonia, epilepsy, dysmorphism, term SGA, Ebstein anomaly | arr1p36.33p36.22(82154_1160306)x1 | 11.5Mb | unknown | 1p36 deletion syndrome (OMIM# 607872) |
| 22/F/5y8m | GDD, hypotonia, dysmorphism | arr9p24.3p22.3(203,861-14,831,003)x1 | 14.6Mb | unknown | Chromosome 9p deletion syndrome (OMIM# 158170) |
| 23/M/3y8m | ASD | arr16p12.2(21,620,625-21,740,274)x1 | 120Kb | unknown | Chromosome 16p11.2 deletion syndrome593 KB (OMIM# 611913) |
| 24/F/19m | ASD, dysmorphism | arr17q24.2(65,738,331-66,344,703)x1 | 606Kb | maternal (294Kb) | BPTF gene (not affected in mother) PMID: 22166941 (16) |
| 25/M/6y8m | Mild ID, dysmorphism, epilepsy, macrocephaly, prematurity | arr15q13.2q13.3(30,940,398-32,922,947)x1 | 2Mb | unknown | 15q13.3 deletion syndrome (OMIM# 612001) |
| 26/F/3y | GDD, hypotonia, microcephaly, epilepsy, dysmorphism, | 1-arr1q21.2(147391614-147826658)x3<br>2-arr17p13.1(7082687_7277907)x1* | 1-435 Kb<br>2- 195Kb | 1- maternal (102 Kb)<br>2- de novo | 2*Chromosome 17p13.1 deletion syndrome (OMIM# 613776) |

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