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The Development Aspect of Children with Delayed Development between Patients with or without CNVs

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Introduction
Microarray-based comparative genomic hybridization (array CGH) has been widely adopted as a valuable clinical diagnostic test for children with delayed development. Bradley P Coe et al. suggested copy number variants (CNVs) are associated with many neurocognitive disorders. Patients with CNVs may present with varying clinical features, but presented with delayed development, it is more likely CNV played a role in the manifestation of symptoms. Hence, it would be meaningful to compare the clinical development aspect of children suspected of delayed development between patients with or without copy number variations.

Objective
To compare and analyze the clinical development aspect of children suspected of delayed development between patients with or without Copy Number Variations (CNV).

Method
A retrospective chart review was done in 65 children who underwent array CGH after visiting PM&R Department outpatient clinic with delayed development as chief complaints. Children were evaluated for Denver Developmental Screening Test (DDST), Sequenced Language Scale for Infants (SELSI)/Preschool Receptive-Expressive Language Scale (PRES). Data were collected from January 2016 to November 2017. A Mann-Whitney U test was conducted to determine statistical differences of Developmental Quotient (DQ), Receptive Language Quotient (RLQ) and Expressive Language Quotient (ELQ) between two groups: 19 children with CNVs and 46 children without CNVs.

Results
Of 65 children who underwent array CGH after visiting PM&R Department outpatient clinic with delayed development as chief complaints, average age was 34 months (mean age 34±25.3) and 19 patients (29.2%) had copy number variations (Table 1, 2). Among CNV (+) group, 14 children underwent DDST; among CNV (-) group, 29 children underwent DDST. Among variables, gross motor scale was significant lower (p=0.0381) in CNV (+) group compared with CNV (-) group (Table 3). Among CNV (+) group, 5 children underwent either SELSI or PRES; among CNV (-) group, 27 children underwent above language assessment examination. Both receptive and expressive language scores did not reveal significant difference between two groups.

Conclusion

Of children with delayed development who took array CGH, 29.2% were diagnosed with CNVs. The gross motor domain in DQ was significantly lower in children with CNV compared to children without CNV. This result suggests that additional genetic factors may contribute to this variability. Active detection of genomic imbalance could play some vital role when presented with prominent gross motor delay in children with delayed development.

Table 1. General demographics

	(N=65)
Age (months)	34 ± 25.3
Gender (male : female)	40 : 25
DDST Developmental Quotient	(N=43)
Personal social	63.6 ± 20.4
Fine motor	71.1 ± 19.9
Gross motor	64.0 ± 19.1
Language	57.1 ± 22.1
SELSI or PRES	(N=32)
Receptive Language Quotient	49.6 ± 20.6
Expressive Language Quotient	47.9 ± 17.2

Values are presented as mean ± standard deviation
DDST, Denver Developmental Screening Test; SELSI, Sequenced Language Scale for Infants; PRES, Preschool Receptive-Expressive Language Scale

Table 2. Array-CGH results and clinical features of the 19 patients with CNVs

Patient	Age (months)	Gender	Array result	Size	Inheritance	Clinical features
1	8	M	arr[hg19]8q21.11q21.13(76,069,471_81,532,974)x1	5.5 Mb	de novo	DD, DLD, Facial dysmorphism, Simian crease, Abnormal patterns of toes, Neonatal hypotonia
2	2.5	M	arr[hg19]12p13.33p11.1(450,479_34,345,585)x3~4	33.9 Mb	Unknown	DD, Dextroversion of the heart, ICH, Hypotonia
3	48	F	arr[hg19]14q13.3q21.1(36,747,497_42,447,650)x1	5.7 Mb	Maternally inherited	DD, DDH, ID, Spastic diplegia, Hypotonia
4	0.9	F	arr[hg19]4q35,1q35.2(185,274,461_190,469,337)x1, 10p15.3p11.23(148,206_29,975,521)x3	5.2 Mb and 30 Mb	Unknown	DD, Cardiomegaly, ASD secundum with septal aneurysm, Severe hypotonia, Congenital arachnoid cyst
5	42	M	arr[hg19]13q12.3(30,656,355_31,905,182)x3	1.2 MB	Unknown	DD, DLD, Hyperactivity, Bronchomalacia, ID, ASD, Facial dysmorphism, Hypotonia
6	22	M	arr[hg19]21q21.1(20,090,068_22,116,178)x1	2.0 Mb	Unknown	DD, Congenital hypotonia, Pes planus, Ataxic gait, Hypotonia
7	13	F	arr[hg19]15 q11.2q13.1(23,739,358_29,213,461)x1	5.5 Mb	Unknown	DD, Severe hypotonia, DDH
8	18	M	arr[hg19]1q21.1q21.2(146,564,743-149,224,043)x1	2.7 Mb	Unknown	DD, DLD, HIE, Ataxic gait, Planovalgus, Hammer toe
9	34	M	arr[hg19]8p23.2(3,710,810-5,922,013)x3	2.2 Mb	Unknown	DD, DLD, Facial dysmorphism, Hypotonia
10	60	F	arr[hg19] Xp22.33p22.2(61091_10125133)x1	10 Mb	Unknown	DD, DLD, Facial dysmorphism, Moderate ID
11	36	F	arr[hg19] 16p11.2(29673954_30197341)x3	523 kb	Unknown	DD, DLD, Epilepsy, Severe ID, Facial dysmorphism
12	48	F	arr[hg19] 17q12(34817422_36168104)x3	1.4 Mb	Unknown	DD, DLD
13	17	F	arr[hg19] 9q33.2q33.3(124628147_127176303)x1	2.5 Mb	de novo	DD, Inguinal hernia, Hypotonia
14	72	M	arr[hg19] 3q29(195740357_197395697)x1	1.7 Mb	Unknown	DD, DLD, Exotropia
15	16	M	arr[hg19] 16p12.3p11.2(16899617_28574419)x3	11.7 Mb	de novo	DD, Facial dysmorphism, Hyperterlorism, High arched palate, Hypotonia, ID
16	10	F	arr[hg19] 17p11.2(16822683_20193169)x1	3.4 Mb	Unknown	DD, CoA, PDA, Hypotonia
17	9	F	arr[hg19] 12q23.1q23.3 (98731852_104856429)x1	6.1 Mb	Unknown	DD, Cleft lip, Hypotonia
18	48	M	arr[hg19] 15q13.1q13.3 (29213402_32914140)x1	3.7 Mb	Unknown	DD, DLD, ITP
19	19.2	M	arr[hg19] Xp22.31 (6552712_8115153)x3	1.6 Mb	Unknown	DD, Facial dysmorphism, Frontal boldness, Hypotonia, High arched palate

DD, Delayed development; DLD, Developmental language delay; ID, Intellectual disability; DDH, Developmental dysplasia of the hip; HIE, Hypoxic-Ischemic Encephalopathy; ITP, Idiopathic thrombocytopenic purpura; CoA, Coarctation of aorta; PDA, Patent ductus arteriosus

Table 3. Comparison between the groups classified by copy number variations

	CNV(+)	CNV(-)
DDST Developmental Quotient	N=14	N=29
Personal social	67.5±17.4	61.7±21.7
Fine motor	69.4±21.1	71.9±19.7
Gross motor	57.7±13.2*	67.1±21.0*
Language	65.9±25.0	52.9±19.7
SELSI or PRES	N=5	N=27
Receptive Language Quotient	47.8±16.9	49.9±21.4
Expressive Language Quotient	51.9±20.6	47.1±16.9

Values are presented as mean ± standard deviation *p <0.05

DDST, Denver Developmental Screening Test; SELSI, Sequenced Language Scale for Infants; PRES, Preschool Receptive-Expressive Language Scale