

Array-Based Comparative Genomic Hybridization in 190 Korean Patients with Developmental Delay and/or Intellectual Disability: A Single Tertiary Care University Center Study

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Purpose: This study analyzed and evaluated the demographic, clinical, and cytogenetic data [G-banded karyotyping and array-based comparative genomic hybridization (array CGH)] of patients with unexplained developmental delay or intellectual disability at a single Korean institution. **Materials and Methods:** We collected clinical and cytogenetic data based on retrospective charts at Ajou University Medical Center, Suwon, Korea from April 2008 to March 2012. **Results:** A total of 190 patients were identified. Mean age was 5.1 ± 1.87 years. Array CGH yielded abnormal results in 26 of 190 patients (13.7%). Copy number losses were about two-fold more frequent than gains. A total of 61.5% of all patients had copy number losses. The most common deletion disorders included 22q11.2 deletion syndrome, 15q11.2q12 deletion and 18q deletion syndrome. Copy number gains were identified in 34.6% of patients, and common diseases among these included Potocki-Lupski syndrome, 15q11-13 duplication syndrome and duplication 22q. Abnormal karyotype with normal array CGH results was exhibited in 2.6% of patients; these included balanced translocation ($n=2$), inversion ($n=2$) and low-level mosaicism ($n=1$). Facial abnormalities ($p<0.001$) and failure to thrive were ($p<0.001$) also more frequent in the group of patients with abnormal CGH findings. **Conclusion:** Array CGH is a useful diagnostic tool in clinical settings in patients with developmental delay or intellectual disability combined with facial abnormalities or failure to thrive.

Key Words: Array CGH, copy number variations, developmental delay, intellectual disability

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INTRODUCTION

The prevalence of intellectual disability (ID) in Asian populations is estimated at 0.25-1.3%.^{1,2} ID and developmental delay (DD) affect not only the patients but also those around them including family and other community members. Conse-

quently, ID/DD is an important issue in public health care. The causes of ID/DD are diverse and include various disorders that affect brain development and function. Although patients with ID/DD receive adequate care from primary care providers, the underlying cause of ID/DD remains poorly understood. Identification of underlying pathogenicity would permit better and more extensive support services, appropriate counseling, and anticipation of possible medical or behavioral complications. However, the proportion of ID/DD cases of unknown etiology is variously reported as 30-60%.^{3,4}

Genetic testing by array-based comparative genomic hybridization (array CGH) has been widely implemented as a promising diagnostic method for patients with unexplained, non-syndromic ID/DD. Array CGH detects genome-wide chromosomal gains or/and losses by semi-quantitative ratio analysis, comparing a patient's DNA to reference DNA simultaneously hybridized to substrate-immobilized probes.⁵ Array CGH provides a much higher resolution than standard chromosomal karyotyping which cannot detect imbalances smaller than 5 Mb, and it enables identification of a greater number of genetic variations.⁶ Copy number variations (CNVs) are characterized as gains or losses in a genomic sequence greater than 1 kb and as alterations in the DNA of a genome. CNVs contribute significantly to genetic variability among different individuals and are increasingly recognized as a causal factor in human genomic disorders. Recent studies suggest that genomic CNVs are important in the etiology of neurodevelopmental disorders, including ID, DD, autism, schizophrenia, and other complex traits.⁷ The detection rate of pathogenic CNVs by array CGH has been reported as 15 to 20% in patients with unexplained ID/DD, which is substantially higher than that obtained with chromosomal karyotyping.⁸⁻¹¹ In the present study, we analyzed demographic, clinical, and cytogenetic data (G-banded karyotyping and array CGH) from patients with unexplained DD/ID at a single institution in Korea.

MATERIALS AND METHODS

We searched for all patients with unexplained DD or ID from Ajou University Medical Center, Suwon, Korea from April 2008 to March 2012. We included patients who underwent karyotyping and array CGH simultaneously. We excluded patients who exhibited abnormal results of previous metabolic, thyroid function or vision/hearing tests or

who had been diagnosed with a brain tumor, brain infection, hypoxic-ischemic encephalopathy, neurocutaneous syndrome or clinically obvious chromosomal syndromes. Clinical data (birth history, family history of neurodevelopmental diseases, growth charts, behavior problems, unprovoked seizure, morphologic abnormalities and major organ anomalies) and cytogenetic data (karyotype and array CGH) were collected based on retrospective chart reviews. Chromosome analysis was conducted with at least a 550-band resolution and described according to the International System for Human Cytogenetic Nomenclature 2009. Whole genome array CGH was performed using commercially available array CGH slides (MACArray Karyo 1440 BAC-chip, Macrogen, Seoul, Korea). The slides contained 1440 human bacterial artificial chromosome (BAC) clones including specific loci for more than 40 chromosomal disorders and 356 cell growth related genes from BAC libraries. Each BAC clone was spaced approximately 2.3 Mb on average across the entire genome and the range of each BAC clone size was 2,421-3,466,361 bp (average 121,708 bp). Each BAC clone was represented on an array as triplicate spots. All arrays were scanned using a GenePix4000B scanner (Axon Instruments, Foster City, CA, USA) and analyzed with array software (MAC VIEWER, Macrogen, Seoul, Korea). The position of the array targets were based on National Center for Biotechnology Information (NCBI) human genome build 37 (GRCh37/hg19; Feb. 2009). After detection of abnormalities by array CGH, we confirmed the microdeletions/duplications by fluorescence *in situ* hybridization (FISH). Ethical approval for this retrospective study was provided by the institutional review board of Ajou University Medical Center, Suwon, Korea (AJIRB-MED-MDB-12-136). Written informed consent was exempted by the board because this was a retrospective study.

Statistical analysis

Statistical analysis was performed using chi-square test and Fisher's exact test. All *p*-values <0.05 were regarded as statistically significant.

RESULTS

A total of 190 (121 males and 69 females) patients, who fulfilled our criteria, were included in this study. The mean age was 5.1±1.87 (range, 0.34-32.0) years. Fifteen patients were small for gestational age. Postnatal failure to thrive (weight-

for-age or height-for-age <3rd centile) was identified in 22 patients and overgrowth (weight-for-age or height-for-age >95th centile) in 6 patients. Eight patients had a family history of neurodevelopment disease. Thirty patients had a history of unprovoked seizures. Morphologic abnormalities^{12,13} were observed in 80 patients: microcephaly (head circumference <3rd centile) in 27, macrocephaly (head circumference >95th centile) in seven, brachycephaly in eight, dolichocephaly in three, plagiocephaly in two, cleft palate in six, facial abnormalities in 55, extremity abnormalities in 16, cryptorchidism in 11 and ambiguous genitalia in one patient. Behavioral problems were combined in 27 patients and included autistic features (n=15), aggressive behaviors

(n=6), and hyperactive and attention deficit behaviors (n=6). Major organ anomalies were confirmed in 20 patients: congenital heart disease (n=19) and unilateral renal agenesis (n=1). Congenital heart diseases consisted of atrial septal defect (n=7), ventricular septal defect (n=6), patent ductus arteriosus (n=4), pulmonary stenosis (n=2), tetralogy of fallot, coarctation of the aorta, aortic stenosis, bicuspid aortic valve, and idiopathic hypertrophic subaortic stenosis (n=1, respectively). Demographic and clinical characteristics are summarized Table 1.

Array CGH yielded abnormal results in 26 of 190 patients (13.7%). Of the 26 patients with abnormal CGH, 10 patients (n=10/26, 38.5%) showed normal karyotype. The

Table 1. Clinical Characteristics of 190 Patients

Trait	n (%)	
Sex (male : female)	121 : 69 (1.75 : 1)	
Age (yrs)	5.1±1.87 (range, 0.34-32.0)	
Clinical features	All patients had unexplained intellectual disability & developmental delay	
	Small for gestational age	15 (7.9%)
	Family history of neurodevelopment disease	8 (4.2%)
	Postnatal failure to thrive	22 (11.6%)
	Overgrowth	6 (3.2%)
	Behavior problems	27 (14.2%)
	Unprovoked seizure	30 (15.8%)
	Morphologic abnormalities ^{12,13}	80 (42.1%)
	Microcephaly/Macrocephaly	34 (17.9%; 27/7)
	Brachycephaly/Dolichocephaly/Plagiocephaly	13 (6.82%; 8/3/2)
	Cleft palate	6 (3.2%)
	Facial abnormalities	55 (29.0%)
	Asymmetric/Coarse/Elongated/Triangular-shaped face	6 (1/2/2/1)
	Metopic ridge/Frontal bossing	2 (1/1)
	Ptosis	6
	Epicanthi/Blepharophimosis	4 (3/1)
	Antimongoloid slant palpebral fissures	3
	Hypertelorism	5
	Micrognathia	2
	Macrostomia/Pouting mouth	5 (3/2)
	Microtia/Large ears/Dysplastic ears/Low-set ears	8 (1/2/1/4)
	Others	32
	Extremities abnormalities	16 (8.4%)
	Talipes equinovarus	3
	Pes planus	4
	Syndactyly/Polydactyly	3
	Joint contracture/Hip joint dislocation/Joint hypermobility	4 (2/1/1)
	Clinodactyly	3
	Cryptorchidism	11 (5.8%)
	Ambiguous genitalia	1
	Major organ anomaly	20 (10.5%)
	Congenital heart disease	19 (10%)
	Renal agenesis	1

other 16 patients presented with array CGH results consistent with conventional karyotype analysis.

Sixteen patients (n=16/26, 61.5%) exhibited a heterozygous loss (deletion): 22q11.2 deletion syndrome (n=4), Angelman syndrome (n=3), 18q deletion syndrome (n=2), Williams-Beuren syndrome, Smith-Magenis syndrome, Wolf-Hirschhorn syndrome, 18p deletion syndrome, 3p deletion syndrome, 2q deletion and 13q deletion (n=1, respectively). Patients 5, 6, and 7 were diagnosed with Angelman syndrome, with a 2.06-Mb deletion of 15q1.2-q12. Heterozygous gains were identified in 8 patients (34.6%): Potocki-Lupski syndrome (n=2), 15q11-13 duplication syndrome (n=2), duplication 22q (n=2), Cat Eye syndrome, duplication 13q and Klinefelter syndrome (n=1, respectively). Patient 17 showed simultaneous deletion of Xp22.31 and duplication of Yq11.2. These abnormal karyotype findings are summarized in Table 2.

Abnormal karyotype with normal array CGH was exhibited in 5 patients: balanced translocation (n=2), inversion (n=2) and low-level mosaicism (n=1). These abnormalities are summarized in Table 3.

Morphologic abnormalities were significantly more frequent ($p<0.001$) in patients with abnormal array CGH than in patients with normal array CGH results. Facial abnormalities ($p<0.001$) were also more frequent in the group with abnormal CGH. The other morphologic abnormalities, including microcephaly ($p=0.430$), cleft palate ($p=0.155$), and extremity abnormalities ($p=0.622$), showed no significant difference between the two groups. Failure to thrive ($p=0.005$) was more frequent in patients with abnormal CGH. No statistically significant differences were found for being small for gestational age ($p=0.458$), family history of neurodevelopment disease ($p=0.649$), overgrowth ($p=0.180$), behavioral problems ($p=0.854$), unprovoked seizure ($p=0.570$) and congenital heart disease ($p=0.091$).

All parents of the patients who had abnormal array CGH results had normal phenotype. Cytogenetic analysis of the parents was not performed, except for the parents of patient 18 (*de novo*), because most of the parental samples were not available.

DISCUSSION

Genetic tests are recommended for unexplained ID/DD as they can provide diagnostic and prognostic information and allow precise genetic counseling for families with an affect-

ed child. For decades, G-banded karyotyping has been the standard first-tier test for detection of genetic imbalance. In recent years, clinical evidence supporting the use of array CGH for unexplained ID/DD has increased and array CGH is now commercially available in the clinical setting.⁸ Array CGH provides a remarkably higher resolution compared to conventional karyotyping, revealing submicroscopic deletions and duplications.¹⁴⁻¹⁶ Several studies anticipate that array CGH will become a routine method in patients with ID/DD, replacing routine karyotyping.^{8,11,17} The present study, for first time at a single institute in Korea, evaluated the diagnostic yield of array CGH in patients with unexplained ID/DD.

A meta-analysis of 33 studies on patients with ID, autism spectrum disorders, or multiple congenital anomalies indicated an average diagnostic yield for array CGH of 12%.¹⁸ In our study, the rate of abnormal findings was 13.7% and this appeared to be consistent with previous studies.^{4,8,19,20} Morphologic abnormalities, especially facial abnormalities, and failure to thrive were significantly more frequent in patients with abnormal array CGH than in patients with normal array CGH. Therefore, we discerned that patients with ID/DD accompanied by facial abnormalities or failure to thrive would generate a higher diagnostic value for array CGH.

In this study, we also perceived that copy number losses were about twice as frequent as gains; losses were identified in 61.5% and gains in 34.6% of patients. Because most copy number changes arise by non-allelic homologous recombination (NAHR), both loss and gain events arising from NAHR should occur at similar rates theoretically. However, microdeletion syndromes have been reported more often than microduplication syndromes in patient groups with ID/DD clinically. Several possibilities might explain why copy number losses are detected more often than gains in patients with ID/DD. Horev, et al.²¹ advocated that deletions exerted a more severe effect than duplications on phenotype, including viability, brain structure, and behavior, in mice. Moreover, Shchelochkov, et al.²² reported that microduplications show milder phenotypes such as subtle dysmorphic facial features, internal organ anomalies, and neuropsychological abnormalities than microdeletions in humans. In this context, we also identified more copy number losses than gains. We agree with previous reports that gains are clinically under-diagnosed due to relatively milder or absent ID/DD. Although ID/DD patients with mild phenotypes may be under-diagnosed, array CGH can help doctors to identify

Table 2. Results of Abnormal Array CGH

Pt. No.	Age	Clinical feature (in addition to DD & ID)	Type of aberration	Karyotype	NCBI build 37.1	Size (Mb)	Genes (No.)	Syndrome	Previous case reports
1	3.6	Morphologic abnormalities, congenital heart disease (TOF)	Del	46,XY	Arr 22q11.21 (19,030,620-19,861,970)×1	0.83	22	22q11.2 deletion syndrome [#188400]	
2	24.1	Morphologic abnormalities, articulation disorder	Del	46,XX	Arr 22q11.21 (19,030,620-19,861,970)×1	0.83	22	22q11.2 deletion syndrome [#188400]	
3	5.5	SGA, torticollis	Del	46,XX	Arr 22q11.21 (19,030,620-19,861,970)×1	0.83	22	22q11.2 deletion syndrome [#188400]	
4	3.7	Hypocalcemia	Del	46,XY	Arr 22q11.21 (19,030,620-19,861,970)×1	0.83	22	22q11.2 deletion syndrome [#188400]	
5	1.9	Unprovoked seizure, morphologic abnormalities, ataxic gait	Del	46,XY,inv(9)(p11q13),del(15)(q11.2q12)	Arr 15q11.2q12 (24,970,734-27,026,553)×1	2.06	45	Angelman syndrome [#105830]	
6	2.9	Unprovoked seizure, microcephaly	Del	46,XY	Arr 15q11.2q12 (24,970,734-27,026,553)×1	2.06	45	Angelman syndrome [#105830]	
7	1.3	Happy mood, morphologic abnormalities, febrile status epilepticus	Del	46,XX	Arr 15q11.2q12 (24,970,734-27,026,553)×1	2.06	45	Angelman syndrome [#105830]	
8	0.4	Morphologic abnormalities, FTT, congenital heart disease (PS), sleep problem	Del	46XY,inv(9)(p11q13)	Arr 7q11.23 (73,577,309-73,789,051)×1	0.21	7	Williams-Beuren syndrome [#194050]	
9	2.9	Aggressive behavior problem, morphologic abnormalities	Del	46,XY,del(7)(p11.2p11.2)	Arr 17p11.2 (17,083,225-19,654,341)×1	2.57	15	Smith-Magenis syndrome [#182290]	
10	6.2	Microcephaly, SGA, FTT, repetitive hand movements	Del	46,XY	Arr 4p16.3 (1,814,926-2,050,532)×1	0.24	7	Wolf-Hirschhorn syndrome [#194190]	
11	1.3	Morphologic abnormalities, FTT, corpus callosum dysgenesis	Del	46,XX,del(3)(p25)	Arr 3p25.3 (8,938,984-9,719,604)×1	0.78	5	3p deletion syndrome [#613792]	
12	1.3	Morphologic abnormalities	Del	46,XX,del(18)(q21.3)	Arr 18q21.32qter (56,585,988-74,727,265)×1	18.14	21	18q deletion syndrome [#601808]	
13	1.8	Morphologic abnormalities, hypotonia, umbilical hernia	Del	46,XY,del(18)(q22)	Arr 18q22.1qter (66,226,796-74,727,265)×1	8.50	7	18q deletion syndrome [#601808]	
14	1.1	Unprovoked seizure, morphologic abnormalities, microcephaly, SGA, FTT, hyperopia, nystagmus	Del	46,XX,del(18)(p11.2)	Arr 18p11.31p11.22 (4,335,713-10,810,013)×1	6.47	4	Del(18)(p11.2p11.3) [#146390]	

Table 2. Continued

15	1.4	Morphologic abnormalities, congenital heart disease (PDA), microcephaly	Del	46,XY,r(13)(p13q34)[19]/46,XY,dic r(13;13)(p13q34;p13q34)[1]	Arr 13q34 (110,442,026-114,266,156)×1	3.82	8	Del(13)(q34)	Huang, et al. ²⁴
16	3.3	Morphologic abnormalities, FTT, cryptorchidism	Del	46,XY,der(2)del(2)(q14;1q22.1)(2;6)(q35;q23.3),der(6)t(2;6)(q35;q23.3)	Arr 2q14;1q22.1 (116,143,366-138,356,329)×1	22.21	12	Del(2)(q14;1q22.1)	None
17	12.6	ADHD, FTT	Del+dup	46,Y,der(X)t(X;Y)(p22.3;q11.2)	Arr Xp22.31p22.33 (2,772,135-7,177,016)×1, Yq11.22q11.23 (17,028,334-26,291,320)×3	4.50 (del) 9.26 (dup)	4 (del) 29 (dup)	Xp22 deletion syndrome [#300830]	
18	3.2	Morphologic abnormalities	Dup	46,XY	Arr 17p11.2 (17,575,978-17,824,623)×3	0.25	4	Potocki-Lupski syndrome [#610883]	
19	17.1	None	Dup	46,XY	Arr 17p11.2 (17,575,978-19,654,341)×3	2.08	11	Potocki-Lupski syndrome [#610883]	
20*	13.2	Unprovoked seizure, family history of neurodevelopment	Dup	47,XX,+mar	Arr 22q13.31qter (44,443,600-51,036,432)×3	6.59	20	Dup(22)(q13.31 pter)	Frye ²⁵ Peeters, et al. ²⁶
21*	14.4	Morphologic abnormalities, family history of neurodevelopment	Dup	46,XY,add(9)(q34)	Arr 22q13.31qter (44,443,600-51,036,432)×3	6.59	20	Dup(22)(q13.31 pter)	Frye ²⁵ Peeters, et al. ²⁶
22	9.8	Autistic spectrum disorder, morphologic abnormalities, pigmentation of skin, scoliosis	Dup	Mos47,XX,+mar[38]/46,XX[2]	Arr 15q11.2q12 (24,970,734-27,026,553)×3	2.06	45	15q11-13 duplication syndrome [#608636]	
23	15.0	Family history of neurodevelopment	Dup	46,XY	Arr 15q11.2q12 (24,970,734-27,026,553)×3	2.06	45	15q11-13 duplication syndrome [#608636]	
24	0.5	Morphologic abnormalities, congenital heart disease (ASD), unilateral kidney agenesis, micropenis, hydronephrosis	Dup	47,XY,+mar	Arr 22q11.1q11.2 (17,473,112-18,519,155)×3	1.05	29	Cat Eye syndrome [#115470]	
25	1.4	Morphologic abnormalities, microcephaly, FTT, congenital heart disease (PDA, BAV)	Dup	46,XX,der(5)(5;13)(p15.3;q14.2)	Arr 13q14.2q34 (47,283,313-114,266,156)×3	66.98	40	Dup(13)(q14.2q34)	Machado, et al. ²⁷
26	2.1	Unprovoked seizure		47,XXY	Arr Xpterqter (2,772,135-154,109,712)×2			Klinefelter syndrome	

DD, developmental delay; ID, intellectual disability; TOF, tetralogy of fallot; SGA, small for gestational age; FTT, failure to thrive; PS, patent ductus arteriosus; PDA, attention deficit hyperactivity disorder; ASD, atrial septal defect; BAV, bicuspid aortic valve; CGH, comparative genomic hybridization.
*Siblings.

Table 3. Result of Abnormal Karyotype with Normal Array CGH

Pt. No.	Age	Clinical feature (in addition to DD & ID)	Type of aberrations	Karyotype	Array	Previous case reports
27	6.4	Morphologic abnormalities, failure to thrive, congenital heart disease (PDA)	Mos	47,XX,+14[7]/46,XX[23]	Arr(1-22,X)×2	Shinawi, et al., ²⁸ von Sneider and Lacassie ²⁹
28	0.5	Unprovoked seizure, microcephaly, failure to thrive	t	46,XX,t(5;21)(q26.1;q22.3)	Arr(1-22,X)×2	
29	6.6	Autistic spectrum disorder, unprovoked seizure, failure to thrive	Inv	46,XY,inv(9)(p11q13)	Arr(1-22,X)×2	-
30	25.8	Schizophrenia, torticollis	t	46,XX,t(9;11)(p22;p15.3)	Arr(1-22,X)×2	
31	4.2	Morphologic abnormalities, congenital choanal atresia	Inv	46,XX,inv(2)(p23q21)	Arr(1-22,X)×2	

DD, developmental delay; ID, intellectual disability; PDA, patent ductus arteriosus; CGH, comparative genomic hybridization.

and elucidate cytogenetic abnormalities, increasing the diagnostic yield thereof.

In our study, patients 5, 6 and 7 had gene dosage changes of 2.06 Mb size on chromosome 15. Only one patient, patient 5, showed abnormal results in karyotyping, even at the same resolution. Standard karyotyping can only detect large chromosomal aberrations over 5-10 Mb in size, and fails to detect small regions of amplification or deletion. In addition, interpretation of a karyotype is labor intensive and highly dependent upon the experience and skill of the cytogeneticist. Array CGH provides a relatively high throughput and highly automated data interpretation, and requires no hands-on work per sample after initiation of the assay run. Therefore, we consider that chromosomal genetic testing with array CGH has additional merits as a diagnostic method, when compared with G-banded karyotyping, only in patients with unexplained ID.

On the other hand, an abnormal karyotype with normal array CGH was found in 2.6% (n=5/190) of patients in this study: balanced translocation (n=2), inversion (n=2) and low-level mosaicism of trisomy 14 (n=1). The inability of array CGH to detect balanced structural abnormalities is well known. One patient (patient 27) showed low-level mosaicism (estimated percentage of mosaicism was 23.3%) of trisomy 14 confirmed by karyotyping, but this was not detected by array CGH alone. The ability of array CGH to detect low-level mosaicism is not completely known. Based on a literature review, array CGH is unable to detect abnormal cell mosaicism at a frequency below 20-30%.²³ Although the association of these chromosome structural changes and low-level gene dosage changes with abnormal phenotypes is controversial, this is important information for genetic counseling. Karyotyping is still a useful tool for supplementing the limitations of array CGH technology.

As we mentioned previously, CNVs have been shown to be associated with a wide variety of developmental and neurocognitive syndromes. Although array CGH has several limitations, it is sufficiently precise that clinical implementation of array CGH provides additional information on causative genetic diseases in patients with unexplained DD or ID. We also expect that array CGH, complemented by karyotype analysis, would be a useful diagnostic tool in selected patient groups, especially those with ID/DD combined with craniofacial anomaly or failure to thrive.

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