



# Clinical utility of chromosomal microarray analysis to detect copy number variants: Experience in a single tertiary hospital

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**Purpose:** To summarize the results of chromosomal microarray analysis (CMA) for copy number variants (CNVs) detection and clinical utility in a single tertiary hospital.

**Materials and Methods:** We performed CMA in 46 patients over the course of two years. Detected CNVs were classified into five categories according to the American College of Medical Genetics and Genomics guidelines and correlated with clinical manifestations.

**Results:** A total of 31 CNVs were detected in 19 patients, with a median CNV number per patient of two CNVs. Among these, 16 CNVs were classified as pathogenic (n=3) or likely pathogenic (LP) (n=11) or variant of uncertain significance (n=4). The 16p11.2 deletion and 16p13.11 deletion classified as LP were most often detected in 6.5% (3/46), retrospectively. CMA diagnostic yield was 24.3% (9/37 patients) for symptomatic patients. The CNVs results of the commercial newborn screening test using next generation sequencing platforms showed high concordance with CMA results.

**Conclusion:** CMA seems useful as a first-tier test for developmental delay with or without congenital anomalies. However, the classification and interpretation of CMA still remained a challenge. Further research is needed for evidence-based interpretation.

**Key words:** Chromosome microarray analysis, Copy number variations, Developmental disability, Genetic testing, High-throughput nucleotide sequencing.

## Introduction

Genetic diseases are caused by genomic aberrations in single nucleotide variations leading to structural changes including deletion, duplication, and translocations. G-banded chromosome analysis is a standard method to detect chromosome

abnormalities, but it is limited in its sensitivity, since it only detects structure abnormalities  $\geq 3$ -10 Mb [1]. On the other hand, chromosomal microarray analysis (CMA) is an excellent method for detecting microdeletions or duplications  $< 400$  kb [2]. In addition, CMA can be more useful because the interpretation of G-banded assay depends on the examiner's experience whereas

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**Table 1.** Clinical characteristics of 37 patients with clinical features

Patient no.	Age	Sex	Clinical symptoms	Congenital anomaly	Familial history
S1	8 D	M	Developmental delay, epilepsy	Cleft palate	-
S2	2 M	M	Epilepsy	Cortical malformation	-
S3	3 Y	F	Developmental delay	Horseshoe kidney	Febrile seizure in aunt
S4	14 D	F	Hypotonia	-	-
S5	3 Y	M	Developmental delay	-	-
S6	8 Y	M	Developmental delay	-	-
S7	5 Y	M	Developmental delay	Facial dysmorphism	-
S8	25 D	F	Developmental delay	Aniridia, macrocephaly	Aniridia in father
S9	27 D	F	Epilepsy, small for gestational age, respiratory distress	Hemivertebra	-
S10	22 D	M	Developmental delay, epilepsy	-	-
S11	20 D	M	Developmental delay	-	-
S12	5 M	F	Developmental delay, epilepsy	-	-
S13	9 M	F	Developmental delay	-	Low height in brother
S14	5 Y	M	Developmental delay	Microcephaly, retinal degeneration	Visual impairment in mother
S15	4 Y	M	Developmental delay, epilepsy	-	Seizure in aunt
S16	3 Y	M		Flat feet	Club foot in brother
S17	12 Y	F	Asthma	Pulmonary agenesis	-
S18	4 Y	F	Developmental delay	Strabismus	Strabismus in uncle
S19	4 Y	M	Developmental delay	-	-
S20	2 Y	M	Developmental delay	Dysmorphic face	-
S21	5 Y	M	Developmental delay	-	-
S22	2 Y	M	Developmental delay	-	-
S23	12 Y	M	Developmental delay, epilepsy	-	-
S24	5 Y	M	Developmental delay, epilepsy	-	Febrile seizure in father
S25	35 Y	F	Recurrent abortion	-	-
S26	0 M	M	Low birth weight, hypothyroidism, hypocalcemia	-	-
S27	1 Y	M	Developmental delay, epilepsy	Dolicocephaly, nystagmus	-
S28	18 Y	M	Common variable immunodeficiencies	-	-
S29	1 Y	M	Developmental delay, epilepsy	-	-
S30	4 M	M	Nephrogenic diabetes insipidus, developmental delay	-	-
S31	2 Y	M	Developmental delay, epilepsy	Facial dysmorphism, macrocephaly	-
S32	2 Y	M	Developmental delay	-	-
S33	1 M	M	Epilepsy	Hydranencephaly	-
S34	3 Y	M	Developmental delay	-	-
S35	3 Y	M	Epilepsy	Atrial septal defect	-
S36	18 M	F	Developmental delay	-	-
S37	13 Y	F	Developmental delay	-	Developmental delay in father

D, day; M, month; Y, year; M, male; F, female; -, not remarkable.

CMA does not. Therefore CMA is a primary approach for copy number variant (CNVs) detection [3], whose clinical usefulness has been reported in clinical practices aimed to detect specific developmental delays [4].

However, CNVs is common in the healthy population and reported in about 35% of people [2,5]. By 2015, over 2.3 million

CNVs were reported in the database of genomic variants [6], and the number of CNVs is expected to increase further with the commercialization of new CMA and next-generation sequencing (NGS) techniques. Therefore, an accurate interpretation of variants is required, and it is important to evaluate laboratory methods and correlation with clinical phenotypes [7]. To deter-

**Table 2.** Chromosomal microarray analysis results in 19 patients

Patient No. <sup>a</sup>	Age	Sex	Region/tier	Size	Included Online Mendelian Inheritance in Man gene	Origin
S1	8 D	M	arr 1p32.3(54,898,830-55,347,872)×3 [LB]	449 kb	ACOT11, TTC4, PARS2, DHCR24	N/A
S2	2 M	M	arr 1p33(49,843,336-50,439,863)×1 [LB] 22q12.2q12.3(32,097,481-32,206,553)×1 [VUS]	596 kb	DEPDC5 (22q12.2q12.3)	N/A
S3	3 Y	F	arr 2p16.3(51,240,308-51,375,539)×1 [LP] 13q34(111,584,492-115,107,733)×1 [LP] 13q31.3q34(92,03,882-111,584,453)×3 [LP]	3.5 Mb 19.6 Mb	ARHGFE7, SOX1, ATP11A, MCF2L2, F7, F10, PROZ, PCID2, CUL4A, LAMP1, ADPRH1, TFDP1, ATP4B, GRK1, GAS6, RASA3, CDC16, UPF3A (2p16.3); GPC5, GPC6, DCT, GPR180, SOX21, ABCC4, DZIP1, DNAJC3, GPR183, TM9SF2, CLYBL, ZIC2, PCCA, GGA2, MALCCN, ITGBL1, FGF14, TPP2, METTL21C, COL4A1, COL4A2, CARKD, CARS2 (13q31.3q34)	Paternal : 2p16.3 deletion
S4	14 D	F	arr 4p15.31p15.2(20,440,445-21,317,234)×3 [LB]	876 kb	SLIT2, KCNIP4	N/A
S5	3 Y	M	arr 7q11.23(72,700,524-74,147,166)×3 [P] Yq11.223(24,215,168-24,985,431)×0 [LB]	1.4 Mb 12.5 Mb 770 kb	NSUN5, TRIM50, FKBP6, FZD9, BAZ1B, BCL7B, TBL2, MLXIP, VPS37D, WBSOR22, STX1A, ABHD11-AS1, CLDN3, CLDN4, WB-SCR27, WBSOR28, ELN, LIMK1, EIF4H, MIRS90, LAT2, RFC2, CLIP2, GTF2IRD1, GTF2I (7q11.23); PRY2, PRY, TTTY6, TTTY5 (Yq11.223);	N/A
A1	3 M	F	arr 8p23.2p23.1(2,432,599-7,044,046)×3 [VUS] 8p23.1(10,249,776-11,935,465)×3 [LP]	1.7 Mb	CSMD1, MCPHI, ANGPT2, AGPAT5, DEFB1, DEFA4, DEFA1, DEFA3, DEFA5, MSRA, PRSS55, RP11, SOX7, PINX1, MIMMR9, SLC33G5, FAM167A, BLK, GATA4, NEIL2, FDF1, CTSB	N/A
S6	8 Y	M	arr 8p23.1(158,048-10,949,033)×1 [LP]	10.8 Mb	FBXO25, DLGAP2, CLN, ARHGFE10, MYOIM2, CSMD1, MCPHI, ANGPT2, AGPAT5, DEFB1, DEFA6, DEFA1, DEFA3, DEFA5, DEFB103B, SPAG11B, FAM9047P, FAM90410P, DEFB4A, CLDN23, MFHAS1, EFI1, PPP1R3B, TMKS, MIR124-1, MSRA, 8PRSS55, RP11, SOX7, PINX1	N/A
S7	5 Y	M	arr 10q11.22(46,287,821-47,015,529)×1 [B] 21q22.11(34,844,796-35,189,393)×1 [LP]	727 kb 344 kb	FAM21C, SYT15, GPRIN2 (10q11.22); GART, SON, DONSON, CRYZL1, ITSM1 (21q22.11)	N/A
A2	4 M	F	arr 11p11.2(51,126,723-51,579,695)×3 [B] 18p11.31p11.22(6,635,754-9,557,565)×3 [VUS]	439 kb 934 kb	OR4C46 (11p11.12); ARHGAP28, LANMA1, PTPRM, MTCL1, NDUJF2, ANKRD12, TWSG1, RALBP1, PPP4R1 (18p11.3p11.22)	Paternal: 18p11.31p11.22 duplication
S8	25 D	F	arr 11p14.3(25,201,603-25,695,000)×1 [LB] Xp22.33(327,827-1,262,136)×1 [P]	453 kb 2.9 Mb	SHOX	N/A
S9	27 D	F	arr 15q11.2(24,348,989-24,811,184)×3 [B] 16p11.2(29,580,020-30,177,240)×1 [LP]	462 kb 597 kb	PWRN2, PWRN1 (15q11.2); SPN, QPRT, KIF22, MAZ, PRRT2, PAGR1, MVP, CDIPT, KCTD13, TAOK2, HIRIP3, DOC2A, FAM57B, ALDOA, PPP4C, TBX6, YPEL3, MAPK3 (16p11.2);	N/A
S10	22 D	M	arr 16p11.2(29,567,295-30,240,227)×1 [LP]	672 kb	SPN, QPRT, KIF22, MAZ, PRRT2, PAGR1, MVP, CDIPT, KCTD13, TAOK2, HIRIP3, DOC2A, FAM57B, ALDOA, PPP4C, TBX6, YPEL3, MAPK3, CORO1A, SULT1A3, SULT1A4 (16p11.2)	N/A
A3	7 M	M	arr 16p11.2(29,567,295-30,177,999)×1 [LP] 21q21.1(20,195,201-21,203,900)×3 [B]	610 kb 1.0 Mb	SPN, QPRT, KIF22, MAZ, PRRT2, PAGR1, MVP, CDIPT, KCTD13, TAOK2, HIRIP3, DOC2A, FAM57B, ALDOA, PPP4C, TBX6, YPEL3, MAPK3 (16p11.2)	N/A
A4	4 M	F	arr 16p11(29,432,212-30,177,916)×3 [LP]	745 kb	BOLA2, SLX1A, SLX1B, SPN, QPRT, KIF22, MAX, PRRT2, OAGR1, MVP, CDIPT, KCTD13, TAOK2, HIRIP3, DOC2A, FAM57B, ALDOA, PPP4C, TBX6, YPEL3, MAPK3 (16p11.2)	De novo
A5	1 M	M	arr 16p13.11(14,897,372-16,516,109)×1 [LP]	1.6 Mb	NOMO1, NPIPA1, PDXD1C1, NTANI, RRN3, KIAA0430, NDE1, MYH11, ABCC1, ABCC6, NOMO3 (16p13.11);	N/A

Table 2. Continued

Patient No. <sup>a</sup>	Age	Sex	Region/tier	Size	Included Online Mendelian Inheritance in Man gene	Origin
S11	20 D	M	arr 16p13.11(14,897,372-16,513,078)×1 [LP] 17q12(37,278,506-38,061,667)×3 [VUS]	1.6 Mb 783 kb	NOMO1, NPIP1, PDXDC1, NTAN1, RRN3, KIAA0430, NDE1, MYH11, ABCC1, ABCC6, NOMO3 (16p13.11); PLXDC1, CACNB1, RPL19, RBXL120, MED1, CDK12, NEUROD2, PPP1R1B, STARD3, PNMT, PGAP3, ERBB2, MIEN1, GRB7, IKZF3, ZPBP2, GSDMB (17q12)	N/A
A6	2 M	F	arr 16p13.11(15,318,664-16,309,165)×1 [LP] 16p13.11p12.3(16,730,374-18,172,468)×1 [LB]	990 kb 1.4 Mb	KIAA0430, NDE1, MYH11, ABCC1, ABCC6 (16p13.11); XYL11 (16p13.11p12.3)	N/A
A7	2 M	F	arr 17p12(14,087,933-,15491,532)×3 [P]	1.4 Mb	COX19, HS3ST3B1, PMP22, TEK13, CDR11 (17p12)	Paternal: 17p12 duplication
S12	5 M	F	arr Xp11.3p11.2(43,994,132-52,832,596)×3 [LP]	8.8 Mb	EFHC2, FUNDCT1, DUSP21, KDM5A, MIR221, MIR222, KRBOX4, ZNF674, CHST7, SLC9A7, RP2, JADE3, RGN, NDUFB11, RBM10, UBA1, INE1, TBC1D25, RBM3, WDR13, WAS, SUV39H1, GATA1, HDAC6, DERAS, PCSK1N, TIMM17B, PQBP1, SLC35A2, PIM2, OTUD5, KCND1, GRIPAP1, TFE3, PRAF2, WDR45, PLP22, PRICKLE3, SYP, SSK2, SPANX5 (Xp11.3)	N/A

<sup>a</sup>The "S" indicates patients with clinical feature and "A" indicates patient without clinical features.

D, day; M, month; Y, year; M, male; F, female; LB, likely benign; VUS, variant of uncertain significance; LP, likely pathogenic; P, pathogenic; B, benign; N/A, not available.

mine the classification categories of CNVs, preexisting published literatures and population database according to ethnic groups are valuable evidence [7], so data sharing is a must in this field of research. This study aims to summarize the results of CMA for CNV detection in a single institution and evaluate its clinical usefulness.

## Materials and Methods

This study included 46 patients for whom CMA was requested at the Chungbuk National University Hospital between 2019 and 2020. Peripheral blood samples were collected in ethylenediaminetetraacetic acid tubes. All procedures were performed at Green Cross Laboratories (Yongin, Korea) and performed with CytoScan Dx Assay (Affymetrix Inc., Santa Clara, CA, USA). Human Genome Build 19 was used to perform the description of genomic variants. CNVs were classified into five categories according to the American College of Medical Genetics and Genomics guidelines into pathogenic (P), likely pathogenic (LP), uncertain significance (VUS), likely benign (LB) and benign (B) [7]. This study was approved by the institutional review board of Chungbuk National University Hospital (IRB number: CBNU-2021-03-030).

## Results

Of the 46 patients for whom CMA was requested, 37 had clinical symptoms (patient number S1-S37), among which developmental delay was the most common clinical feature (Table 1). The other 9 patients (patient number A1-A9) were requested based on findings on commercial CNVs neonatal screening test using NGS methods.

A total of 31 CNVs were detected in 19 patients as in Table 2. The median detected indel region size was 934 kb (min 344 kb-max 19.6 Mb), and the median number of detected CNVs per patient was 2 (min 1-max 3). The CNVs were classified as P (n=3), LP (n=14), VUS (n=4), LB (n=6), and B (n=4). Excluding duplicates, there were 17 CNVs classified as P (n=3) or LP (n=10) or VUS (n=4) (Table 3). The 16p11.2 deletion and 16p13.11 deletion classified as likely LP were most often detected in 6.5% (3/46), retrospectively. In particular, the 16p11.2 deletion appears with high frequency in several reports regardless of ethnic, but the 16p13.11 deletion is relatively rare [5,8]. In contrast, 8p23.1 region seems to be a more recurrent region in Korea.

Of all 37 symptomatic patients, 12 patients had one more CNVs. Detected CNVs were classified as P (n=2), LP (n=9), and

**Table 3.** Chromosomal microarray analysis results classified as pathogenic, likely pathogenic and variant of unknowns significance

Regions	ACMG category	Copy number variant related syndrome	Referred critical gene	OMIM #	DECIPHER <sup>a</sup>	This study (n=46)	Korea data [8] (n=617)	United Kingdom [13] (n=420,247)	USA [5] (n=15,749)
<b>Deletion</b>									
2p16.3 deletion	LP	2p16.3 deletion syndrome	<i>NRXN1</i>	#614332	-	1 (2.17%)	-	-	-
8p23.1 deletion	LP	8p23.1 deletion syndrome	<i>GATA4, XKR6</i>	-	+	1 (2.17%)	2 (0.32%)	-	-
13q34 deletion	LP	13q33-q34 deletion syndrome	<i>SOX1, ARHGEF7</i>	#619148	-	1 (2.17%)	-	-	-
16p11.2 deletion	LP	16p11.2 deletion syndrome	<i>KIF22, PRR2, ALDOA, TBX6</i>	#614332	+	3 (6.52%)	6 (0.97%)	104 (0.03%)	67 (0.43%)
16p13.11 deletion	LP	-	<i>MARF1, MYH11</i>	-	+	3 (6.52%)	-	-	-
21q22.11 deletion	LP	ZTTK syndrome	<i>SON</i>	#617140	-	1 (2.17%)	-	-	-
22q12.2q12.3 deletion	VUS	-	<i>DEPDC5</i>	-	-	1 (2.17%)	-	-	-
Xp22.33 deletion	P	-	<i>SHOX</i>	-	-	1 (2.17%)	-	-	-
<b>Duplication</b>									
7q11.23 duplication	P	-	<i>ELN</i>	#609757	+	1 (2.17%)	2 (0.32%)	-	-
8p23.1 duplication	LP	8p23.1 duplication syndrome	<i>CSMD1, GATA4</i>	-	+	1 (2.17%)	1 (0.16%)	-	10 (0.06%)
8p23.2p23.1duplication	VUS	-	<i>CSMD1, GATA4</i>	-	-	1 (2.17%)	-	-	-
13q31.3q34 duplication	LP	-	<i>GATA4, XKR6</i>	-	-	1 (2.17%)	-	-	-
16p11 duplication	LP	16p11.2 duplication syndrome	<i>KIF22, PRR2, ALDOA, TBX6</i>	#614671	+	1 (2.17%)	2 (0.32%)	134 (0.03%)	39 (0.24%)
17p12 duplication	P	Yuan-Harel-Lupski syndrome	<i>PMP22, RAI1</i>	#616652	-	1 (2.17%)	-	237 (0.06%)	15 (0.10%)
17q12 duplication	VUS	-	-	-	-	1 (2.17%)	-	-	-
18p11.31p11.22 duplication	VUS	-	<i>ARHGAP28, LINC00668, LAMA1</i>	-	-	1 (2.17%)	-	-	-
Xp11.3p11.2 duplication	LP	-	<i>SYN1, ZNF8-1, FTSJ1</i>	-	-	1 (2.17%)	-	-	-

<sup>a</sup>Symbol “+” means that CNV listed at DECIPHER CNVs syndromes list (<https://www.deciphergenomics.org/disorders/syndromes/list>).

ACMG, American College of Medical Genetics and Genomics; OMIM, Online Mendelian Inheritance in Man; LP, likely pathogenic; VUS, variant of unknowns significance; P, pathogenic; -, not available.

VUS (n=2) in 10 patients, while 7 LB CNVs were observed in seven patients. In addition, the remaining 25 patients had a normal karyotype without any CNVs. In the asymptomatic group (n=9), detected CNVs were classified as P (n=6), B (n=2), and VUS (n=1) (Fig. 1). Five of the 27 patients with normal CMA findings underwent an additional targeted NGS panel of genes associated with clinical manifestations, but only in three patients additional VUS missense variant were detected. Therefore, it is worth considering follow-up observation or extended whole exome tests for such patients.

## Discussion

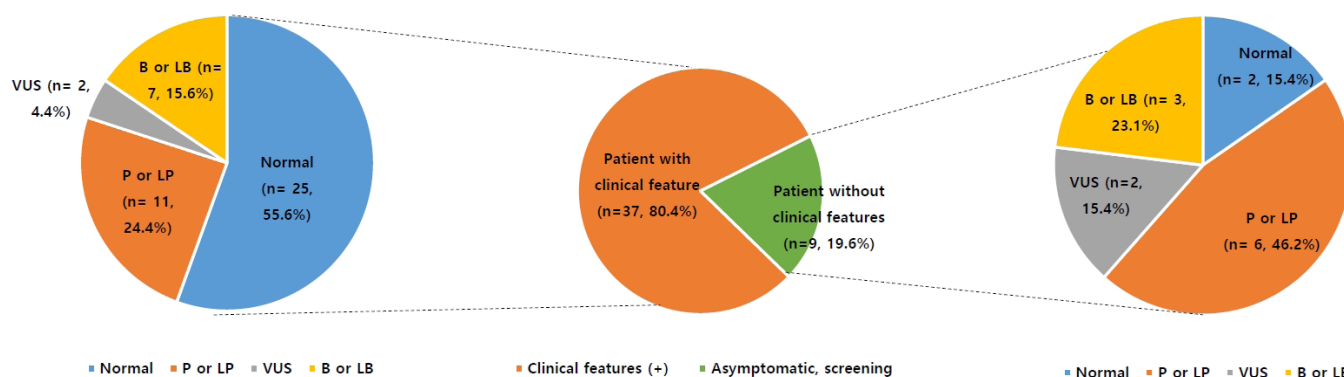
The various clinical manifestations depend on genetic defects; therefore, it is very important to select appropriate diagnostic tools to detect the underlying genetic abnormalities. Recently, several reports have shown it is possible to detect CNV even with NGS, as its detection limit is <300 kb, with a diagnostic sensitivity increasing in proportion to size variations [9,10]. In our study, the result of the newborn screening test using NGS platforms showed high concordance with CMA results, except for two discrepancy cases which showed abnormal findings in NGS but normal in CMA. These CNVs were also actually detected in CMA, but not reported in accordance with our institution's the reporting protocol, which excludes benign CNV less than 400 kb. One case had a suspicious finding of 9q24.3 region 73 kb deletion in NGS, and another case had a suspicious finding of 17p13.3p13.1 region 366 kb duplication in NGS. Therefore, NGS platforms for CNV detection appear to be cost effective and useful as screening test. Nevertheless, because NGS can only detect specific targeted regions, CMA is more comprehensive for all genomic CNVs. In addition, the break point can be confirmed with CMA

clearly.

Similar to previous reports, CMA's diagnostic yield was 24.3% (9/37) for patients with matching P/LP CNVs and clinical symptoms. Most of these patients (S3, S5, S6, S7, S8, S10, S12, and S13) showed global developmental delay, thus confirming CMA's usefulness in the diagnosis of patients with developmental delay. However, in 27 out of 37 symptomatic patients showed normal results in CMA. Although CMA improves diagnostic yield, there are still undiagnosed cases. Consequently, further clinical management guidelines are needed. If a meaningful result is not obtained from CMA, an extended test aimed to a targeted gene panel, whole exome, or whole genome sequencing should be attempted, while the possibility of an inborn metabolic error also should be discussed [11].

As previously known, there was a different effect of deletions or duplications in the same chromosomal position leading to phenotypic differences in clinical expression. In the case of the chromosome 16p11.2, the most frequently detected in our study, although autism spectrum disorder and neurodevelopmental disorder were common clinical manifestation in both deletion and duplication, speech articulation abnormalities and limb and trunk hypotonia were more reported in deletion than in duplication carriers [12]. As for chromosome 16p13.11, also frequently detected in our study, the deletion was classified as pathogenic CNV, while duplication was classified as benign CNV with high frequency and low penetrance [13].

Despite the well-known clinical significance of many CNVs, some findings are often difficult to describe due to the absence of previous reports or different clinical findings from previous reports [7]. Among these, penetrance is a very careful variable to consider in genetic counselling. Despite 16p11.2 deletion and duplication being classified as LP, their penetrances are 62.4%



**Fig. 1.** The classification of CNVs detected in 46 patients requested chromosomal microarray analysis. Possible clinical significance variants including pathogenic (P), likely pathogenic (LP), and variant of unknowns significance (VUS) were 27.0% (10/37) in symptomatic patients and 77.8% (7/9) in asymptomatic or pre-symptomatic patients. B, benign; LB, likely benign.

and 11.2% [14]. However, it is recommended that individuals had P/LP CNVs were regarding presymptomatic status [7]. Therefore, regular development and growth examination test is crucial and, furthermore, medical treatment should be determined through closely monitoring. On the other hand, for variations classified as VUS, there is a possibility of being classified as pathogenic in later, but this is a broad category classification that is more difficult to interpret. Generally they showed inconsistent evidence and it led to classification controversy among laboratories [7]. Many CNVs classified as VUS showed the genotype and phenotype correlation is not clear [8]. For example, the 18p11.31p11.2 duplication detected in asymptomatic patient A2 was classified as VUS, and confirmed as deriving from a healthy father. However, previous studies described that this variation is related to short stature, microcephaly and intellectual delay [15]. Hence, patients and family members should be periodically evaluated through genetic counseling.

In this study, we described CNV frequency with CMA and evaluated its clinical potential in a single tertiary hospital. The classification and interpretation of CMA remained a challenge. However, our study also showed that CMA is a superior method for CNV detection despite the limitation of the small sample size. Further research is needed to establish clinical diagnostic recommendations.

## Authors' Contributions

Conception and design: HSP. Acquisition of data: HSP, KSS, BRS. Analysis and interpretation of data: HSP, AK. Drafting the article: HSP. Critical revision of the article: AK. Final approval of the version to be published: HSP.

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