


Detection of copy number variants with chromosomal microarray in 10 377 pregnancies at a single laboratory

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Abstract

Introduction: Invasive prenatal testing with chromosomal microarray analysis may be a relevant option for all pregnant women, but there is only moderate-quality evidence for such an offer. We intended to study the prevalence of copy number variants (CNVs) in prenatal samples using a single SNP-array platform stratified by indication.

Material and methods: A cross-sectional study was performed based on a cohort. From January 2015 to December 2017, a total of 10 377 prenatal samples were received for prenatal single nucleotide polymorphism (SNP)-array in the laboratory of the Genetics Generation Advancement Corporation. Indications for chromosomal microarray analysis studies included the confirmation of an abnormal karyotype, ultrasound abnormalities, advanced maternal age and parental anxiety. CNVs and region of homozygosity identified by the SNP-array were analyzed.

Results: Of 10 377 cases, 689 had ultrasound abnormalities and 9688 were ascertained to have other indications. The overall prevalence of CNVs was 2.1% ($n = 223/10\ 377$, 95% confidence interval [CI] 1.9-2.4), but the prevalence was 4.4% (95% CI 3.0-6.1) for cases referred with abnormal ultrasound findings and 2.0% (95% CI 1.7-2.3) for other indications. Of the 223 CNVs detected, 42/10 377 were pathogenic (0.4%, 95% CI 0.3-0.6), 84 were susceptibility CNV (0.8%, 95% CI 0.6-1.0) and 97 were variants of uncertain significance (0.9%, 95% CI 0.8-1.1). Using an SNP-based platform allowed for the detection of paternal uniparental disomy of chromosome 14 in a fetus with ultrasound abnormality.

Conclusions: With an indication of advanced maternal age but normal ultrasound scans, the prevalence of pathogenic CNVs was 0.4% and that of susceptibility CNV 0.7%. As CNVs are independent of maternal age, the prevalence is likely the same for younger women. Thus, this study provides further evidence that chromosomal microarray analysis should be available for all women who wish to receive diagnostic testing, as this risk is above the cut-off of 1:300 for Down syndrome, leading to the suggestion of invasive testing. A chromosomal microarray analysis based on SNP-array platform is preferable, as it can also detect uniparental disomy in addition to copy number variants.

Abbreviations: AOH, absence of heterozygosity; AUS, abnormal ultrasound findings; CMA, chromosomal microarray analysis; CNVs, copy number variants; NICHD, Eunice Kennedy Shriver National Institute of Child Health and Human Development; sCNV, susceptibility CNV; SNP, single nucleotide polymorphism; UPD, uniparental disomy; VOUS, variants of uncertain significance.

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KEYWORDS

abnormal ultrasound findings, absence of heterozygosity, copy number variant, pathogenic CNV, prenatal chromosomal microarray analysis, variants of uncertain significance

1 | INTRODUCTION

The development of chromosomal microarray analysis (CMA) has improved the detection of copy number variants (CNVs), which are small genomic deletions and duplications that are not routinely seen in conventional karyotyping. As a first-tier test, CMA offers a much higher diagnostic yield (15%-20%) for genetic testing of children with unexplained developmental delay, intellectual disability, autism spectrum disorders or multiple congenital anomalies not specific to a well-delineated genetic syndrome such as a G-banded karyotype.¹ The Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) funded a large, prospective prenatal study to compare CMA with conventional karyotyping which demonstrated that CMA is more beneficial than karyotyping for fetuses with abnormal ultrasound findings.² In that study, CMA revealed clinically significant CNVs in 6% (45/755) of this group of fetuses.²

In a 2013 systematic review including the NICHD trial (n = 12 362), CMA detected clinically significant CNVs in 6.5% (201/3090) of fetuses with abnormal ultrasound findings and a normal karyotype.³ The American College of Obstetricians and Gynecologists (ACOG) and Society for Maternal-Fetal Medicine (SMFM) recommends (Grade 1A) that CMA should be offered when invasive testing is done in cases with fetal structural anomalies.^{4,5} The prevalence of pathogenic CNVs in cases with referral indications of advanced maternal age and anxiety is 1/210 (0.48%) in a meta-analysis study.⁶ However, CMA cannot precisely interpret the clinical significance of a previously unreported CNV or accurately predict the phenotype of some CNVs associated with variable outcomes.

Several large-scale prenatal microarray studies, systemic review and meta-analyses have compared the diagnostic yields of microarrays and conventional karyotyping.⁷⁻¹² However, the cohorts and systemic reviews have been based on various array platforms from different laboratories with inconsistent reporting criteria. In Taiwan, CMA is a widely accepted option when genetic analysis is performed on invasive samples regardless of the risk factors. In this report, we share our experience with a single nucleotide polymorphism (SNP)-array platform in over 10 000 prenatal samples analysed in our laboratory.

2 | MATERIAL AND METHODS**2.1 | Patients and samples**

Our laboratory provides country-wide service for general population with referrals from clinics, hospitals and medical centers. A total

Key message

According to a single SNP-array platform, the prevalence of pathogenic CNV was 0.4% in fetuses with normal ultrasound scans but advanced maternal age. The use of prenatal chromosomal microarray analysis should be available to all women wishing to receive invasive genetic diagnosis.

of 10 377 prenatal specimens were received for clinical prenatal CMA in the laboratory of the Genetics Generation Advancement Corporation between January 2015 and December 2017. The submitted specimens included (a) amniotic fluid, (b) cultured amniotic cells, (c) uncultured chorionic villus, and (d) cord blood. Informed consent and pretest counseling about the benefits and limitations of the test, the CMA platform, and the possible test results were explained to the patients by medical staff. The indications for CMA studies included:

- abnormal ultrasound findings (AUS),
- high risk of maternal serum Down screening,
- advanced maternal age,
- parental anxiety,
- verification of an already known abnormal fetal karyotype,
- family history of a genetic condition or chromosomal abnormality.

In Taiwan, the Health Promotion Administration (HPA) provides subsidies for prenatal genetic diagnosis for high-risk pregnancies. Therefore, most of the pregnant women beyond 34 years old undergo amniocentesis at 16-18 gestational weeks. It is common for women receiving amniocentesis to be willing to have CMA in addition to karyotyping. Therefore, the indication for the majority of our subjects was advanced maternal age. We describe the prevalence of CMA in a cross-sectional design based on data from an anonymous cohort.

2.2 | DNA extraction

DNA was extracted from uncultured or cultured AF cells using the QIAamp® DNA Blood Mini kits (Qiagen, Hilden, Germany) according to the manufacturer's instructions. The spectrophotometer (BioTek uQuant, Winooski, VT, USA) was used to assess the genomic DNA concentration and purity, according to the manufacturer's protocol.

2.3 | Microarray platform

We carried out DNA copy number detection and genome-wide SNP genotyping on all 10 377 DNA samples with the SNP-array CytoScan 750K (Thermo Fisher Scientific, Chelmsford, MA, USA). The SNP-array CytoScan 750K contains more than 750 000 markers for copy number analysis, of which 550 000 are unique nonpolymorphic oligonucleotide probes and 200 000 are SNP probes that can be used for genotyping. We performed procedures for DNA digestion, ligation, PCR amplification, fragmentation, labeling and hybridization at the Genetics Generation Advancement Corporation Laboratory (Taipei, Taiwan). The raw data from the CEL files obtained through the CytoScan array scanning were analyzed using the software CHROMOSOME ANALYSIS SUITE, versions 3.0 and 3.1 (Thermo Fisher Scientific). The genome annotations were obtained from version GRCH37 (hg19).

2.4 | Data interpretation

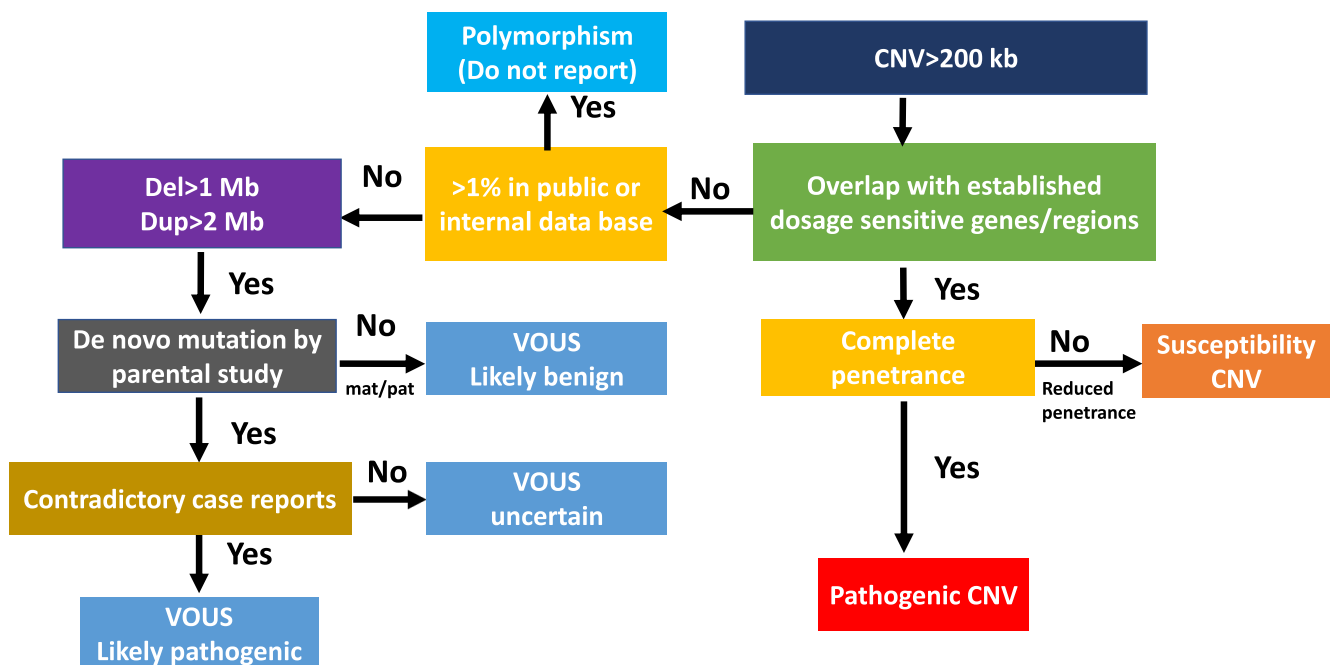
CNVs detected with CMA were aligned with known aberrations in public databases—ClinGen (<http://dbsearch.clinicalgenome.org/search/>), DECIPHER (Database of Chromosomal Imbalance and Phenotype in Humans using Ensembl Resources <https://decipher.sanger.ac.uk/>), ClinVar (<http://www.ncbi.nlm.nih.gov/clinvar/>), Database of Genomic Variants DGV (<http://dgv.tcag.ca/dgv/app/home>), and an internal database of results. The reporting criteria in our laboratory included:

copy-neutral absence of heterozygosity (AOH) of whole chromosome, AOH of chromosome segment larger than 10 megabases (Mb) in chromosomes associated with imprinting disorders (ie chromosomes 6, 7, 11, 14, 15 and 20);

CNVs reported in association with consistent clinical phenotypes across multiple peer-reviewed publications, with well-documented penetrance and expressivity, even if reduced and/or variable; CNVs that overlap completely with an established dosage-sensitive region, and deletion/duplication greater than 200 kb;

a CNV that has been described in a small number of cases in the general population but with insufficient frequency to be considered a polymorphism (> 1%), a CNV that contains a small number of genes that are unknown to be dosage-sensitive or not in the interval, and deletion >1 Mb or duplication >2 Mb. We did not report common benign CNVs as predetermined by internal laboratory standards (Figure 1).

Copy-neutral AOH of the whole chromosome or a segment >10 Mb suggests the presence of uniparental disomy (UPD), in which two copies of chromosomes are both inherited from the same parent, instead of one from each parent. CNVs were classified into three main categories: pathogenic, susceptibility and variants of unknown significance (VOUS). VOUS was further divided into three subcategories: likely pathogenic, uncertain and likely benign. This classification is based on the size and genomic content of CNVs, a review of the literature, and information in available databases. Many CNVs are inherited from unaffected parents. Parental studies are routinely done for CNVs with pathogenic relevance or uncertain clinical significance and may provide additional information regarding their inheritance



Abbreviations: CNV, copy number variants; del, deletion; dup, duplication; mat, maternally inherited; pat, paternally inherited; VOUS, variant of unknown significance.

FIGURE 1 Classifications and reporting of CNVs in prenatal microarray. CNV, copy number variants; del, deletion; dup, duplication; mat, maternally inherited; pat, paternally inherited; VOUS, variant of unknown significance

TABLE 1 Sample demographic data (n = 10 377)

Specimen	Case number	
Uncultured amniotic fluid	10 202	
Cultured amniotic fluid cells	162	
Uncultured chorionic villi	10	
Cord blood	3	
Indication	Maternal age (years)	
Advance maternal age	(37.20 ± 2.74)	7704 (74.2%)
Abnormal ultrasound finding	(31.18 ± 3.38)	689 (6.6%)
High risk maternal serum screening	(31.31 ± 2.99)	462 (4.5%)
Anxiety	(31.68 ± 2.91)	1253 (12.1%)
Others ^a	(32.31 ± 4.04)	269 (2.6%)

^aIncluded family history of a genetic condition or chromosome abnormality, a known abnormal fetal karyotype or microarray result.

and recurrence risk. In addition to fetuses with a known abnormal karyotype, aberrant segments of ≥5 Mb in size were classified as karyotypic abnormalities, whereas aberrations ≤5 Mb in size were classified as submicroscopic CNVs. Although cases may have had more than one CNV, they were counted only once and placed into the category with the most significant clinical relevance. The categories were stratified as pathogenic CNVs, susceptibility CNVs (sCNVs), VOUS-likely pathogenic, VOUS-uncertain and VOUS-likely benign.

2.5 | Statistical analyses

Statistical analyses were performed to determine the statistical differences between the frequencies of CNVs of various indications

using Fisher's exact test, 2-sided test. Values of $P < .05$ were considered statistically significant. The Statistical Package for the Social Sciences for Windows version 24 (SPSS, Chicago, IL, USA) was used for the statistical analyses.

2.6 | Ethical approval

The study protocol was approved by the Joint Institutional Review Board of the Taipei Medical University (#JIRB N201710003, approval date: 12 October 2017), without the requirement of obtaining signed informed consent forms from the study patients.

3 | RESULTS

Table 1 presents data about the prenatal samples (n = 10 377) including specimen type, indications for prenatal testing and the maternal age of each group. Table 2 provides the frequency of abnormal CMA results according to the indication for prenatal diagnosis. Most of the prenatal samples (n = 9970, 96.1%) had a normal result, with no detected changes in copy number. Furthermore, 407/10377 were abnormal and more than half of the abnormal results were undetectable by conventional karyotyping (223/407, 55%). Of the 223 fetuses carrying a CNV, 42 (18%) had a pathogenic CNV, 84 had sCNVs (38%) and 97 had a VOUS (44%). Of these 97 cases with VOUS, 13/97 (13%) were VOUS-likely pathogenic, 18/97 (19%) were VOUS-uncertain and 66/97 (68%) were VOUS-likely benign.

Table 3 shows the recurrent pathogenic CNVs, susceptibility CNVs and the inheritance. Of the 84 sCNVs with incomplete penetrance and variable expressivity, 49 were inherited and 35 were from a de novo event or unknown. Table 4 shows the abnormal CMA

TABLE 2 Frequency of CNV of CMA analysis in 10 377 samples according to CNV size and indication for prenatal diagnosis

Indications for Prenatal diagnosis	Total no. of cases	CNV n (%)	CNV >5 Mb n (%)	CNV <5 Mb			Total n (%) [95%CI]
				Pathogenic n (%)	sCNV n (%)	VOUS n (%)	
Any	10 377	407 ^a (3.9)	185 (1.8)	42 (0.4)	84 (0.8)	97 (0.9)	223 (2.1) [1.9-2.4]
AMA	7704	263 (3.4)	116 (1.5)	28 (0.4)	57 (0.7)	63 (0.8)	148 (1.9) [1.6-2.2]
AUS	689	53 (7.7)	23 (3.3)	7 (1.0)	11 (1.6)	12 (1.8)	30 (4.4) [3.0-6.1]*
MSS	462	28 (6.1)	16 (3.5)	3 (0.7)	4 (0.8)	5 (1.1%)	12 (2.6) [1.5-4.5]
Anxiety	1253	34 (2.7)	12 (0.9)	3 (0.3)	8 (0.6)	11 (0.9%)	22 (1.8) [1.1-2.6]
Other ^b	269	29 (10.8)	18 (6.7)	1 (0.4)	4 (1.5)	6 (2.2%)	11 (4.1) [2.3-7.1]

Abbreviations: AMA, advanced maternal age; AUS, abnormal ultrasound finding; CI, confidence interval; CMA, chromosomal microarray; CNV, copy number variant; MSS, high risk of maternal serum screening; sCNV, susceptibility CNV; VOUS, variant of unknown significance.

^aOne fetus carried both karyotypic abnormality (trisomy X) and a CNV.

^bIncluded family history of a genetic condition or chromosome abnormality, a known abnormal fetal karyotype or microarray result.

*Statistically significant compared with AMA, AUS and anxiety ($P < .001$, Fisher's exact test, 2-sided test).

results including CNVs and AOH subdivided by ultrasound findings. One fetus with AUS was found to have UPD 14 and another had UPD 16. There were 16 fetuses with supernumerary marker chromosomes according to karyotyping and 6/16 were further characterized by CMA (4/9 non-mosaic and 2/7 mosaic). Common autosome aneuploidies were detected in 101 (0.97%) fetuses, including 68 fetuses with trisomy 21 (2 as mosaic), 27 fetuses with trisomy 18, and 6 fetuses with trisomy 13 (one with mosaicism). Sex chromosome abnormalities were identified in 54 (0.52%) cases. The SNP-array was able to detect the lowest level (18%) of 45,X/46,XX mosaicism (Figure 2).

4 | DISCUSSION

As shown in Table 2, CMA revealed karyotypic abnormalities in 185 of 10 377 (1.8% 95% confidence interval [CI] 1.5-2.1) samples. It also found that a large proportion of clinically significant CNVs would have been missed if only conventional karyotyping had been performed (0.4%). CMA provided additional clinical information in 4.6% (32/689) of fetuses with AUS and 2.0% of pregnancies with other indications

for prenatal diagnosis ($P < .001$, Fisher's exact test, 2-sided test). This is comparable to the results of the NICHD study, which showed an increased diagnostic yield over conventional karyotyping of 6% among fetuses with AUS and 1.7% among patients referred for advanced maternal age, parental anxiety and high-risk maternal serum screening.²

A large study involving 5000 fetuses revealed 6.5% detection rate of abnormal CNVs in 2462 cases with structural abnormalities.⁹ The results of two meta-analyses reported detection rates of CNVs of 6.5% and 7% in fetuses, respectively with AUS.^{3,7} The detection of fetuses with AUS was lower in this study (4.6%), which is probably due to most of the ultrasound abnormalities (414/689, 60%) being soft markers for aneuploidy, including choroid plexus cyst, echogenic bowel, intracardiac echogenic foci and single umbilical artery. After excluding common and unspecified sonographic findings, the diagnostic yield of CNVs among fetuses with AUS was found to be 6.2% (14/226; Table 4).

A 2018 report indicated that the frequency of pathogenic and susceptibility CNVs is 2.5% and 1.0% in fetuses with and without AUS, respectively. These results were obtained from two combined cohorts of 18 006 prenatal CMA and are comparable to the

TABLE 3 Recurrent pathogenic and susceptibility copy number variants and the inheritance

Region (gene within region)			Total no. of cases	Inheritance		
Pathogenic CNV	del/dup	Coordinates arr[hg19]		Inherited mat	pat	De novo or NA
17p12 (PMP22)	dup	17p12(14,000,000_15,400,000)*3	7	4	2	1
17p12 (PMP22)	del	17p12(14,000,000_15,400,000)*1	7	1	5	1 ^a
22q11.2 (TBX6)	del	22q11.2(18,600,000-21,800,000)*1	4	0	0	4
Xp22.31 (STS)	del	Xp22.31(6,400,000-8,100,000)*1	3	1	1	1 ^a
7q11.23	del	7q11.23(72650120_74207565)*1	2	0	0	2
Total			23 (0.2%)	6	8	9
Susceptibility CNV						
1q21.1 (RBM8A)	del	1q21.1(145,300,000_145,700,000)*1	3	0	0	3
Distal 1q21.1 (GJA5)	dup	1q21.1(146,000,000_147,800,000)*3	2	0	0	2
Distal 1q21.1 (GJA5)	del	1q21.1(146,000,000_147,800,000)*1	3	2	1	0
15q11.2 (NIPA1)	del	15q11.2(22,700,000_23,200,000)*1	25	10	7	8 ^a
15q13.3 (CHRNA7)	del	15q13.3(32,000,000_32,400,000)*1	2	2	0	0
16p13.11 (MYH11)	dup	16p13.11(14,800,000_16,500,000)*3	22	6	10	6
16p13.11 (MYH11)	del	16p13.11(14,800,000_16,500,000)*1	9	1	3	5 ^a
Distal 16p11.2 (SH2B1)	del	16p11.2(28,800,000_29,000,000)*1	1	0	0	1
Proximal 16p11.2 (TBX6)	dup	16p11.2(29,500,000_30,100,000)*3	4	1	0	3
Proximal 16p11.2 (TBX6)	del	16p11.2(29,500,000_30,100,000)*1	4	0	0	4
16p13.3 (CREBBP)	dup	16p13.3(3,700,000_3,900,000)*3	1	0	0	1
17q12 (HNF1B)	dup	17q12(34,800,000_36,200,000)*3	2	1	0	1
22q11.2 (TBX1)	dup	22q11.2(18,600,000_21,400,000)*3	6	1	4	1
Total			84 (0.8%)	24	25	35

del/dup, deletion/duplication; NA, not available.

^aThe inheritance of CNV was not available in one case.

TABLE 4 Classifications of ultrasound abnormalities and abnormal CMA results in 689 fetuses

Ultrasound findings	Case Number	Abnormal CMA result	CNV >5 Mb	CNV <5 Mb			AOH
				pCNV	sCNV	Vous	
Total	689	55	23	7	11	12	2
Ultrasound soft marker							
Choroid plexus cyst	132	6	1	2	1	2	0
Echogenic intracardiac foci	213	12	4	1	2	4	1 ^a
Echogenic bowel	55	2	0	0	1	1	0
Single umbilical artery	14	2	0	0	1	1	0
Subtotal	414	22	5	3	5	8	1
Structural anomaly							
Central nervous system	27	0	0	0	0	0	0
Cardiovascular system	58	6	0	2	2	2	0
Gastrointestinal system	11	2	2	0	0	0	0
Genitourinary system	30	3	2	0	1	0	0
Respiratory system	4	0	0	0	0	0	0
Musculoskeletal system	17	3	0	1	0	2	0
Head/face	16	2	1	0	1	0	0
Cystic hygroma/hydrops fetalis	7	3	3	0	0	0	0
NT >3.5 mm	44	7	5	0	2	0	0
Chest	9	0	0	0	0	0	0
Abdominal wall defect	2	2	2	0	0	0	0
Multiple anomaly	1	1	0	0	0	0	1 ^b
Subtotal	226	29	15	2	7	4	1
Non-structural anomaly							
Amniotic fluid	8	1	0	1	0	0	0
Placenta	3	0	0	0	0	0	0
IUGR	2	0	0	0	0	0	0
Not specified	36	3	3	0	0	0	0
Subtotal ^a	49	4	3	1	0	0	0

AOH, absence of heterozygosity; CMA, chromosomal microarray; CNV, copy number variant; IUGR, intrauterine growth restriction; NT, nuchal translucency.

^a UPD 16. ^bUPD 14 of paternal origin.

rates of 2.6% and 1.1% (1:90) in our study.¹³ A recent meta-analysis of pooled cohort studies assessing CMA in 10 614 fetuses found pathogenic CNV in 0.48% of cases referred for advanced maternal age or parental anxiety.⁶

The risk of CNVs is independent of maternal age,⁶ therefore we can assume that the 0.4% prevalence we find in our study in women of advanced maternal age would also be found in younger women. Hereby all women have a risk of abnormal findings above 1:300, which is the usual cut-off for offering invasive testing for Down syndrome testing. Taken these points together, we suggest that CMA should be offered to all pregnant women undergoing invasive prenatal testing regardless of the referral indications.

An increasing number of sCNVs are identified as risk factors for neurodevelopmental disorders including autism spectrum disorders, developmental delay, intellectual disability and psychiatric

problems. In the postnatal setting, candidates for testing are ascertained because of specific clinical features. In the prenatal setting, however, many pathogenic features such as neurocognitive ability are not readily observed, or only become apparent at a later gestational age. Nevertheless, the prevalence of sCNV was 0.8% (95% CI 0.7-1.0) in all prenatal samples, 1.6% (95% CI 0.9-2.8) among those with ultrasound abnormalities and 0.8% (95% CI 0.6-0.9) among those without them. In a prenatal cohort, SNP-array analysis showed that a higher incidence of sCNV in fetuses with ultrasound abnormalities than that of fetuses without ultrasound anomalies, 2.6% (27/1033) vs 1.35% (18/1330), respectively.^{14,15} The frequency observed in our study was lower, which could possibly be related to the less complicated ultrasound findings and larger number of cases studied (Table 4). The incomplete penetrance of sCNV provide difficult prenatal dilemmas, as not all

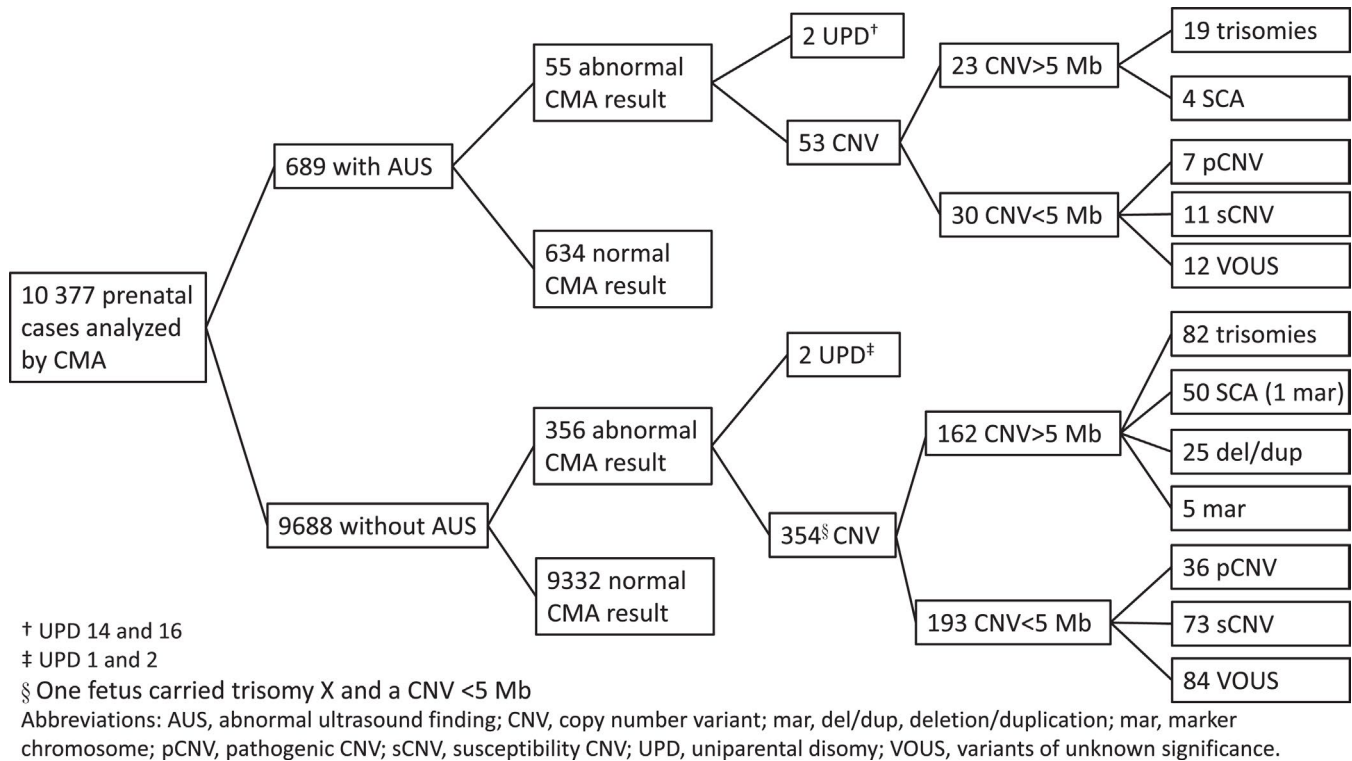


FIGURE 2 Cytogenomic profile of cases with vs without abnormal ultrasound as an indication. †UPD 14 and 16. ‡UPD 1 and 2. §One fetus carried trisomy X and a CNV < 5 Mb. AUS, abnormal ultrasound finding; CNV, copy number variant; del/dup, deletion/duplication; mar, marker chromosome; pCNV, pathogenic CNV; sCNV, susceptibility CNV; UPD, uniparental disomy; VOUS, variants of unknown significance

women are interested in such results¹⁶ and counseling in these situations is difficult.¹⁷⁻²⁰

A challenge for clinical laboratories offering diagnostic CMA is discerning the pathogenicity of CNVs. The VOUS are genetic changes that are not commonly seen in the population, so little or no clinical evidence is available to assess their pathogenicity. In our study, VOUS were observed in 0.9% (95% CI 0.8-1.1) of all prenatal samples, 1.7% (95% CI 1.0-3.0) of fetuses with ultrasound abnormalities, and 0.8% (95% CI 0.7-1.1) of fetuses without ultrasound abnormalities (Table 2). Most of the VOUS were inherited (75/97, 78%) and were categorized as likely benign. Hillman et al reported a VOUS rate of 1.4% when all testing indications were considered.⁷ This finding is consistent with the re-evaluation of the interpretation of CNVs in the NICHD study, in which there was a reduction in the VOUS rate to 0.9% based on new literature and public data sharing.^{21,22}

Although most CMA results are straightforward, a proportion of results including sCNV, VOUS-likely pathogenic and VOUS-uncertain (1%) are not clear-cut and pre-test knowledge of these issues greatly facilitates post-test delivery.^{13,23} Explanations should be provided for the concept of phenotypic heterogeneity and for the severity of a condition, which may range from apparently normal to severe. When such a condition is encountered, patients should be aware that the clinical spectrum of the disorder may not be predictable in their fetus and that they themselves could possibly carry the same CNV, despite showing no obvious clinical phenotype.

Prenatal diagnosis of sCNV increases parental anxiety. However, the finding may be considered valuable information because it raises the physician's awareness about the identification of and early intervention for neurodevelopment disorders, resulting in improved outcomes for affected children. Nevertheless, the limitation of our study included incomplete information about the karyotype results and a lack of information on pregnancy outcomes and postnatal long-term follow up of the children carrying CNVs.

Currently two major microarray platforms exist in prenatal diagnosis—comparative genomic hybridization (CGH)-based array and SNP-based array. The former is used to detect CNV at different resolutions with various array platforms and designs. The latter enables the detection of both CNV and copy number neutral regions of AOH suggesting the presence of UPD. The incidence of UPD of any chromosome has been estimated to be 1:3500 live births. UPD of the majority of chromosomes is without phenotypic effect.²⁴ In this cohort, four fetuses (4/10 377) were found to have copy-neutral AOH of whole chromosome involving chromosomes 1, 2, 14 and 16, respectively, indicating UPD. UPD may result from trisomy rescue, which is often associated with placental or fetal mosaicism; therefore, extensive workup of cytogenetic studies is indicated. Genetic counseling regarding recessive disorders of the involved chromosome is also suggested. Therefore, SNP-array is a preferable CMA platform over comparative genomic hybridization-array in the prenatal diagnosis.

5 | CONCLUSION

In this study, prenatal SNP-array analysis was used to detect clinically significant CNVs in fetuses with abnormal ultrasound or pregnancies of advanced maternal age. Although it is impossible to accurately predict the outcome antenatally, we suggest that fetuses carrying sCNV and VOUS may benefit from early identification and intervention programs for neurodevelopment disorders. We also suggest that all women should be offered invasive testing, as all women have a risk of abnormal findings above 1:300. SNP-array analysis also provides genotype information that aids in the diagnosis of triploidy, UPD, occult trisomy mosaicism and parental origin of CNVs, thus improving the interpretation of the results and genetic counseling. Finally, pre- and post-test genetic counseling is critical for implementing prenatal array testing. With patient education and advanced knowledge of phenotype consequences of identified variants, prenatal CMA is expected to become an important diagnostic tool in obstetrical practice.

CONFLICT OF INTEREST

The authors have stated explicitly that there are no conflicts of interest in connection with this article.

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How to cite this article: Lin Y-H, Jong Y-J, Huang P-C, Tsai C. Detection of copy number variants with chromosomal microarray in 10 377 pregnancies at a single laboratory. *Acta Obstet Gynecol Scand.* 2020;00:1-8. <https://doi.org/10.1111/aogs.13886>