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Spectrum of Chromosomal Abnormalities Detected by Chromosomal Microarray in Fetuses with Abnormal Ultrasound Findings: A Prospective Observational Cohort Study

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ABSTRACT

OBJECTIVES: Fetal structural anomalies (FSAs) occur in approximately 3% of pregnancies, increasing perinatal morbidity and mortality. While conventional karyotyping has been a cornerstone of prenatal testing, its limitations in detecting sub-microscopic chromosomal abnormalities necessitate Chromosomal Microarray Analysis (CMA). CMA offers superior resolution, detecting copy number variants (CNVs) undetected by karyotyping. The objectives of the study are to evaluate the diagnostic utility of CMA in fetuses with abnormal ultrasound findings and to determine its additional yield over karyotyping.

STUDY DESIGN: A prospective observational cohort study was conducted at a tertiary care center in South India over 18 months, including 226 singleton pregnancies with fetal structural abnormalities or soft markers. Samples collected via amniocentesis or chorionic villous sampling were analyzed using an Agilent 8x60K array. Results were interpreted based on the GRCh37/hg19 human reference genome, followed by pre- and post-test genetic counseling. Statistical analyses included descriptive and inferential methods.

RESULTS: CMA detected chromosomal abnormalities in 50 cases (17.2%), providing an additional 5.1% diagnostic yield over karyotyping. Common aneuploidies included trisomy 21 (12 cases) and Turner syndrome (6 cases). Notable CNVs were identified in cases with increased nuchal translucency, unossified nasal bones, and central nervous system anomalies. The central nervous system was the most affected (32%), followed by musculoskeletal and cardiovascular systems.

CONCLUSION: CMA enhances the detection of chromosomal abnormalities in fetuses with abnormal ultrasound findings, offering critical insights for prenatal diagnosis and parental decision-making. Genetic counseling remains integral to its application.

Keywords: Chromosomal microarray analysis; Copy number variants; Fetal structural anomalies; Prenatal diagnosis; Ultrasound abnormalities

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Introduction

Fetal structural anomalies (FSAs) detected by ultrasound occur in approximately 3% of pregnancies and can range from isolated anomalies to those involving multiple systems (1). These anomalies increase perinatal mortality and morbidity risks. Invasive prenatal testing has traditionally relied on karyotyping, which, despite its utility, has limitations such as the need for cell culture, lengthy turnaround times, and low resolution (2). Chromosomal microarray (CMA) (3-5) addresses these limitations, offering higher resolution to detect abnormalities as small as 50-100 Kb.

The American College of Obstetricians and Gynaecologists (ACOG) and the Society for Maternal-Fetal Medicine (SMFM) recommend CMA as the first-line test for fetuses with abnormal ultrasound findings (6). CMA detects copy number variants (CNVs), including microdeletions and duplications that conventional karyotyping cannot identify (7-9).

This study aims to evaluate the diagnostic utility of CMA in fetuses with abnormal ultrasound findings to determine the spectrum of chromosomal abnormalities in fetuses with abnormal ultrasound findings detected by CMA and to evaluate the diagnostic yield of CMA. Additionally, the selection of prenatal genetic tests involves multiple factors, including indications for testing, ultrasound findings, and cost-effectiveness, as highlighted in a previous study (10).

Material and Method

This prospective observational cohort study was conducted at a tertiary care specialty-specific perinatal center in south India, done over one and half years after obtaining ethical committee approval (EC Ref No. 10_2020) and the study adhered to institutional guidelines. The inclusion criteria are singleton pregnancies with fetal structural abnormalities, soft markers, early fetal growth restriction, or non-immune hydrops fetalis. Multifetal gestations and CMA performed for other indications were excluded. Informed consent was obtained from all participants. Samples collected through amniocentesis or chorionic villous sampling were analyzed using the Agilent 8×60K array. While structural anomalies were a primary inclusion criterion, soft markers were also considered separately due to their potential association with chromosomal abnormalities. Additionally, informed consent was obtained from all participants for data usage, and the study was conducted by the Declaration of Helsinki.

All the singleton pregnancies with abnormal ultrasound findings in the fetus were offered pre-test genetic counseling. Those who were willing for CMA were included in my study. Samples were obtained either from amniocentesis (16 to 20 ml of amniotic fluid) or chorionic villous sampling (3mg of placental tissue) depending on the gestational age.

Samples were sent to the Department of Medical Genetics, Manipal Hospital, Mangalore. Samples were processed and Chromosomal microarray was performed using an Agilent 8×60K array. This microarray consists of 55077 distinct biological features across the genome, including 3886 unique internal quality control probes. Genomic DNA (400 mg) was used for direct dye labeling using an Agilent Sure Tag DNA labeling kit. The differentially labeled gDNA was purified and hybridized on Agilent 8X60K microarray and then scanned by Agilent Sure Scan microarray scanner. Data was analyzed using Agilent Cyto Genomics v5.0.2.5 Software. The analysis was based on the human reference genome (GRCh37/hg 19). Turnaround time for the test is 3 to 4 weeks. Based on the results of chromosomal microarray patients were offered post-test counseling and follow-up scans accordingly. Data was entered into SPSS software and was analyzed.

The primary outcome variable was the identification of chromosomal abnormalities, including common aneuploidies and copy number variants (CNVs), detected by CMA in fetuses with abnormal ultrasound findings. Secondary outcomes included the additional diagnostic yield of CMA over conventional karyotyping and the distribution of abnormalities across different fetal systems.

Sample size calculation was based on an expected prevalence of chromosomal abnormalities of 7.52%, as per available literature (11,12). The other parameters considered for sample size calculation were 5% absolute precision and 95% confidence level, yielding a required sample size of 112 after accounting for non-participation. The final sample size of 226 was achieved to strengthen the study's statistical power and robustness of findings.

Blinding was maintained during the analysis phase, where the laboratory personnel were blinded to the clinical details of the participants to minimize bias in interpretation.

Data was analyzed using descriptive and inferential statistics. Categorical variables, such as chromosomal abnormalities, were expressed as frequencies and percentages. Continuous variables, such as nuchal translucency measurements, were summarized as means and standard deviations. The additional diagnostic yield of CMA over karyotyping was calculated as a percentage difference. Statistical tests, including chi-square and Fisher's exact test, were used to determine associations between categorical variables. A p-value of <0.05 was considered statistically significant.

Results

The study analyzed 226 participants (Figure 1) (Table I) who underwent CMA testing, revealing significant findings. Increased nuchal translucency (NT) (113) emerged as the most frequent indication for CMA, with CNVs identified in three fetuses whose NT ranged between 3 and 3.5 mm. Among the 21 cases with isolated unossified nasal bone, CNVs were detected in four fetuses, constituting 19% of this subgroup. Central nervous system anomalies were the most prevalent findings, observed in 32% of cases, followed by musculoskeletal and cardiovascular system abnormalities. Overall, CMA detected chromosomal abnormalities in 50 fetuses, translating to a diagnostic yield of 17.2%. This represented a 5.1% additional yield over conventional karyotyping (12.1%). Among the nine cases with multisystem involvement, various chromosomal abnormalities were identified, highlighting the complexity of these conditions. The findings are 1. Pallister-Killian Syndrome (Mosaic Tetrasomy 12p)-Identified in a fetus presenting with increased nuchal translucency (NT) and ventricular septal defect (VSD). Advanced maternal age was a noted risk factor in this case. 2. Wolf-Hirschhorn Syndrome (4p16.3-16.1 Deletion)-A fetus with ventricular septal defect, right aortic arch, and unossified nasal bone was diagnosed with this pathogenic deletion. 3. DiGeorge Syndrome (22q11.2 Deletion)-One fetus exhibited VSD and chamber size discrepancy (left ventricle<right

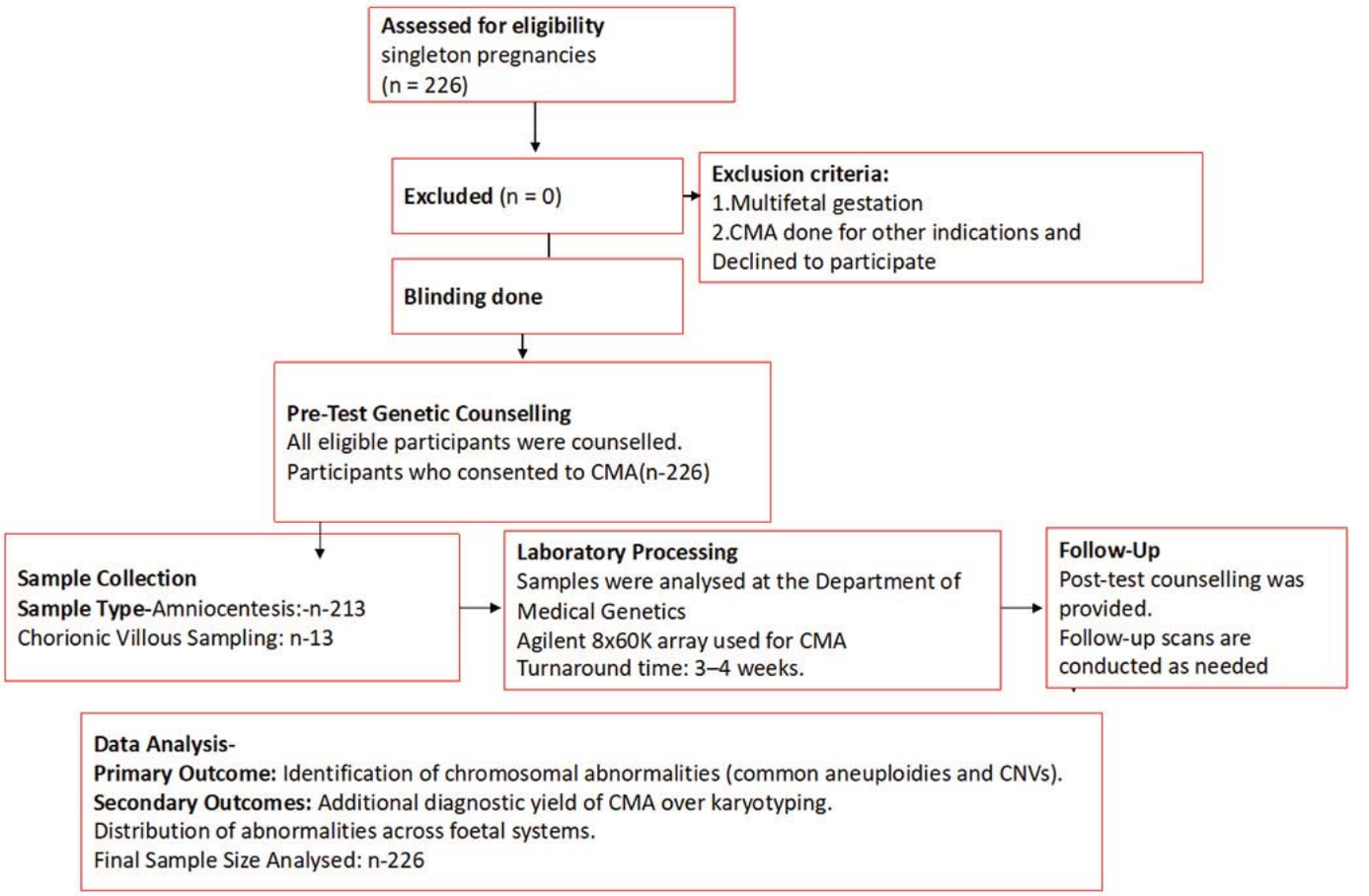

Figure 1: *Participant flow chart (CONSORT flow chart)*

Table I: *Total number of CMA performed with Indications*

Indications	Number
Structural anomalies	
Central nervous system abnormalities	25
Cardiovascular system abnormalities	22
Gastrointestinal system abnormalities	12
Face abnormalities	11
Skeletal system abnormalities	7
Genitourinary system abnormalities	5
Lung abnormalities	1
Soft markers	
Increased nuchal translucency (NT)	113
Unossified nasal bone	21
Increased nuchal fold	6
Non-immune hydrops fetalis (NIHF)	3
Cases with both structural anomalies and soft markers	9

ventricle), confirming the presence of this syndrome. 4. Partial Trisomy 11q-22q-This chromosomal abnormality was found in a fetus with microcephaly and cardiovascular anomalies. 5. 22q11.2 Duplication Syndrome-A fetus with increased nuchal translucency was diagnosed with this duplication, emphasizing the importance of CMA in detecting subtle CNVs. 6. Partial Trisomy 3-A fetus with increased NT and double bubble sign was diagnosed with this abnormality. 7. Chromosome 17 Deletion-Found in a fetus with early-onset fetal growth restriction (FGR), dolichocephaly, and unossified nasal bone, confirming a severe chromosomal defect. 8. Chromosome 8 and 9 Duplication (Likely Pathogenic Variant)-Detected in a fetus with increased NT, suggesting a potential but uncertain clinical significance. 9. 15q11.2 Microdeletion (Variant of Unknown Significance). Two fetuses were identified with this microdeletion. One had increased NT and an unossified nasal bone. The other had increased NT without additional markers.

These findings reinforce the role of CMA in detecting submicroscopic chromosomal abnormalities that may not be evident through conventional karyotyping alone. Multisystem abnormalities have a higher likelihood of harboring pathogenic CNVs, underscoring the need for comprehensive genetic evaluation in such cases.

The chromosomal abnormalities detected included common aneuploidies and notable CNVs (Tables II and III). Common aneuploidies encompassed trisomy 21 (12 cases with increased NT), trisomy 18 (5 cases), trisomy 13 (1 case), and Turner syndrome (6 cases). Significant CNVs included a 2809.64 Kb duplication on chromosome 22q11.21, a 3751.69 Kb deletion on chromosome 2q37.3, and a mosaic tetrasomy of the 12p13.33-p11.1 region. These findings were statistically significant, as demonstrated by the chi-square test ($p<0.05$), confirming a strong association between specific ultrasound abnormalities and CNVs. The additional diagnostic yield pro-

Table II: *Distribution of chromosomal abnormalities by category*

Category	T21	T18	T13	Turner	XYY	XXY	Microdeletions	Microduplications
Structural Anomalies	4	1	0	0	0	0	3	1
Soft Markers Only	15	2	0	5	0	0	4	3
Both Structural & Soft Markers	3	1	0	1	0	1	3	0

T21-Trisomy 21 (Down syndrome), T18-Trisomy 18 (Edwards syndrome), T13-Trisomy 13, Turner-Turner syndrome, XYY- XYY syndrome, XXY-Klinefelter syndrome

Table III: *Defects and associated copy number variants*

Defect seen	Copy number variants
Increased NT	2230.388KB deletion in chromosome 4 (4q27-q28.1) –VUS
Increased NT	partial trisomy of 11q23.3-q25 and 22q11.1-q11.21
Increased NT	28623.213kb and 4041.223kb duplication in chromosome 8 (8q23.3-q24.3) and chromosome 9 (9q34.2-q34.3)- likely pathogenic
Unossified nasal bone	3751.69Kb deletion of chromosome 2 (2q37.3)- pathogenic 1018.76Kb duplication of chromosome 1 (1p12)- VUS
Unossified nasal bone	2809.64Kb duplication of chromosome 22q11.21- pathogenic
Unossified nasal bone	1.01Mb heterozygous deletion in chromosome 3- likely pathogenic
Unossified nasal bone	Long contiguous stretch of homozygosity on chromosome 4 –VUS
U/L cleft lip palate	1.5- to 3.0-Mb heterozygous deletion of chromosome 22 (22q11.2) – pathogenic
VSD	1391.822Kb mosaic deletion in chromosome 22 (22q11.2) – pathogenic
Early onset fetal growth restriction, unossified nasal bone, VSD, right aortic arch	8042.284Kb deletion of chromosome 4 (4p16.3-p16.1 region)- pathogenic
Increased NT, VSD	34115.165 duplication of chromosome 12 (12p13.33-p11.1 region)- mosaic tetrasomy- pathogenic
Double bubble sign + anechoic posterior fossa cyst increased NT	Partial trisomy 3p
FGR+ hyperechogenic bowel	A long contiguous stretch of chromosome 3-VUS
FGR + Unossified Nasal Bone	1330.295 KB Deletion in chromosome 17(17p12)- pathogenic
Increased NT, tricuspid regurgitation	Deletion in chromosome 15

NT: Nuchal translucency, VSD: Ventricular septal defect, FGR: Fetal growth restriction, VUS: Variant of uncertain significance

vided by CMA underscores its utility in prenatal diagnosis for detecting sub-microscopic chromosomal alterations that karyotyping may miss. To maintain clarity, soft markers, and structural anomalies were analyzed distinctly to ensure an accurate assessment of their contributions to the diagnostic yield.

Discussion

This study demonstrates the effectiveness of Chromosomal Microarray Analysis (CMA) in detecting sub-microscopic deletions and duplications in fetuses with abnormal ultrasound findings. The additional yield of CMA over karyotyping, at 5.1%, is consistent with previous studies. Central nervous system anomalies were the most identified, followed by musculoskeletal and cardiovascular system anomalies. This study underscores the importance of CMA in cases such as unossified nasal bones, where 19% of such cases revealed Copy Number Variants (CNVs) that were undetectable by karyotyping. Furthermore, a study conducted to analyze how to choose prenatal genetic testing (10) emphasizes that genetic testing should be selected based on multiple parameters, including ultrasound abnormalities, prior screening results, and family history. The higher prevalence of CNS anomalies in our cohort contrasts with findings from another study (13), which reported cardiovascular anomalies as the most common. These differences could be attributed to population variations and differences in ultrasound screening practices.

In a multicentre systematic review and a retrospective analysis (14,15) done on Chromosomal Microarray Analysis in Fetuses wherein they concluded that the cardiovascular system was the most affected system, whereas our study found the central nervous system (32%) to be the most frequently involved, followed by the musculoskeletal and cardiovascular systems. These differences suggest that regional variations in prenatal diagnostic protocols and access to advanced imaging techniques may influence the types of abnormalities detected in different populations. Further studies should explore the impact of genetic background and environmental factors on the prevalence of CNVs in different organ systems.

In addition to structural anomalies, soft markers such as increased nuchal translucency (NT) and unossified nasal bone play a critical role in risk assessment for chromosomal abnormalities. Our study reinforces the importance of these markers, particularly in cases where NT measurements range between 3-3.5 mm. While this threshold is considered a lower risk in some clinical guidelines, our findings indicate that even mild NT increases may be associated with significant CNVs. This aligns with previous research highlighting the diagnostic value of CMA in cases with borderline NT measurements, where conventional screening methods may underestimate chromosomal abnormality risks (16).

The 22q11.21 deletion syndrome (DiGeorge syndrome) was the most common CNV observed in fetuses with cardiovascular anomalies in a retrospective study using chromosomal microarray analysis in fetuses (14). Similarly, DiGeorge syndrome was reported in two cases in our study, one with Ventricular Septal Defect (VSD) and another with cleft lip and palate. Notably, in our cohort, we observed a strong association between microdeletion syndromes and congenital heart defects, reinforcing previous evidence that CNVs play a crucial role in fetal cardiac development. This suggests that CMA should be strongly considered in cases with isolated or complex congenital heart defects, even in the absence of other major ultrasound markers.

Isolated nuchal translucency was the most common indication for CMA in our study. CNVs were detected in only three fetuses with increased nuchal translucency, specifically in those with NT measurements of 3-3.5 mm. A study done using Chromosomal microarray in fetuses with increased nuchal translucency reported 12.8% CNVs in fetuses with NT greater than 3.5mm (16). This suggests that a re-evaluation of current NT cutoffs for recommending CMA may be warranted, particularly in cases where additional ultrasound markers are present. Clinicians should consider integrating CMA into risk stratification models to optimize detection rates for pathogenic CNVs.

In another study done on the Performance of chromosomal microarray for patients with intellectual disabilities/developmental delay, autism, and multiple congenital anomalies (17), the pathogenic CNV rate was 4.4% in fetuses with NT less than 5mm, compared to 11.1% greater than 5mm. This emphasizes the importance of postnatal follow-up for fetuses with negative CMA results, as some CNVs may manifest later in life with neurodevelopmental disorders. Future research should investigate the long-term neurodevelopmental outcomes of fetuses with variants of unknown significance (VUS) detected during prenatal CMA.

Furthermore, the presence of multiple system anomalies significantly increased the likelihood of pathogenic CNVs in our cohort. This highlights the need for a tiered approach to prenatal genetic testing, where cases with isolated findings may undergo stepwise testing, while those with multisystem involvement warrant comprehensive CMA as a first-line investigation. Our study contributes to the growing body of evidence advocating for CMA as a superior diagnostic tool compared to karyotyping in the prenatal setting.

Strengths and Limitations: This study reinforces the clinical utility of CMA, demonstrating its role in improving detection rates, refining risk assessment, and supporting informed reproductive choices.

The smaller sample size may have limited the generalizability of the findings. Chromosomal microarray analysis (CMA) was not able to detect balanced chromosomal arrangements, low-level mosaicism, point mutations, exonic deletions and duplications, or methylation defects. Counseling parents regarding variants of unknown significance posed challenges due to their uncertain clinical implications. Furthermore, incorporating perinatal pathological findings and pregnancy outcomes could have enhanced diagnostic yield by allowing more precise phenotypic and genotypic matching.

Conclusion

Chromosomal Microarray Analysis (CMA) improves the detection of sub-microscopic chromosomal abnormalities in fetuses with abnormal ultrasound findings, offering a higher diagnostic yield than karyotyping. This study highlights the clinical relevance of CMA, particularly in cases with unossified nasal bone, increased nuchal translucency (NT>3 mm), structural anomalies, and multiple soft markers.

Given its superior resolution, CMA should be integrated into routine prenatal testing, especially for high-risk pregnancies. Comprehensive genetic counseling is essential to guide parental decision-making, particularly when variants of uncertain significance (VUS) are identified. While CMA has limitations, advancing genomic technologies like whole-exome sequencing (WES) may further enhance prenatal diagnostics.

Declarations
Acknowledgments: We thank the Department of Medical Genetics, Manipal Hospitals, for their collaboration and all study participants for their involvement.
Conflict of interest: nil
Ethics approval and consent to participate: All participants provided written informed consent for the use of their data. The study was reviewed and approved by the ethics committee [Registration No: ECR/933/Inst/TG/2017] (Ethics approval reference number: 10_2020, dated 17-03-2020). All procedures were conducted in accordance with the principles of the Declaration of Helsinki.
Availability of data and materials: The data supporting this study is available through the corresponding author upon reasonable request.
Competing interests: The authors declare that they have no

competing interests.

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Authors' Contributions: This study was conducted and written following the CRediT (Contributor Roles Taxonomy) guidelines. Each author contributed to the study as follows: Conceptualization: SR, RP: Data curation: PM, GN: Formal Analysis: RP: Funding Acquisition: Not applicable; Investigation: SR, PM: Methodology: SR, RP: Project Administration: SR: Resources: RP, GN: Software: Not applicable; Supervision: SR: Validation: RP: Visualization: PM: Writing - Original Draft: SR, RP: Writing - Review & Editing: SR, RP, PM, GN: All authors have read and approved the final version of the manuscript.

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