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Epidemiology of fetal cerebral ventriculomegaly and evaluation of chromosomal microarray analysis versus karyotyping for prenatal diagnosis in a Chinese hospital

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Abstract

Objective: To evaluate the efficiency and incremental value of chromosomal microarray analysis as compared with standard karyotyping for the identification of genomic abnormalities in fetal DNA.

Methods: This retrospective study enrolled female patients with ultrasonographically diagnosed fetal ventriculomegaly. The prevalence, associated anomalies and clinical outcomes of ventriculomegaly were evaluated based on data from a single maternal and child health hospital in southwest China.

Results: A total of 943 cases of ventriculomegaly were analysed in this study, which were diagnosed at a mean ± SD gestational age of 23.8 ± 8.2 weeks. Non-isolated ventriculomegaly cases had a significantly higher maternal age than isolated cases (29.6 ± 5.5 versus 27.9 ± 4.2 years, respectively) and were also associated with a larger proportion of bilateral (56.1% versus 46.7%, respectively) and severe (12.8% versus 3.7%, respectively) ventriculomegaly. There were

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97 cases detected by both karyotyping and microarray analysis. All apparent chromosome abnormalities identified upon karyotyping were detected with the use of microarray analysis. Microarray analysis also reported genetic abnormalities in 20 additional cases not detected by karyotyping. Of these additional 20 cases, 9.3% of pregnancies reported standard genetic variants for clinically relevant information, whereas 11.3% reported uncertain genetic abnormalities.
Conclusion: Chromosomal microarray analysis is an efficient tool, significantly increasing the diagnostic power for prenatal diagnosis.

Keywords
Prenatal diagnosis, fetal cerebral ventriculomegaly, ultrasonographic scan, karyotype, chromosomal microarray analysis

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Introduction

Chromosomal microarray analysis of copy-number variants (CNVs) is recommended as a first-tier clinical diagnostic test, giving an indication of intellectual and developmental delay in prenatal diagnosis.[1,2] Compared with current karyotyping, microarray analysis provides incremental value for the identification of genomic abnormalities in fetal DNA.[3] As reported, it can identify up to 20% additional genetic causes in fetuses accompanying structural anomalies.[4]

Ventriculomegaly is a common fetal brain anomaly that can be diagnosed by routine ultrasonographic examination after 15 weeks of pregnancy.[5] The normal width of the fetal lateral ventricular atrium is of a constant size <10 mm. Measurements above this cut-off are defined as mild (10–12 mm), moderate (13–15 mm) and severe (>15 mm) fetal ventriculomegaly.[6] After ultrasonographic screening, standard karyotyping and microarray analyses are performed to determine the genomic pathogenesis for women with prenatally detected ventriculomegaly.

Ultrasound findings provide clues to investigate founder mutations in standard karyotyping and microarray analysis.[7] Currently, the growing use of microarray analysis has identified additional clinically-significant cytogenetic information compared with karyotyping, but it also yields findings of uncertain clinical significance or genetic variants causing adult-onset disorders.[8] This current study evaluated the prevalence, associated anomalies, clinical outcomes and efficacy of microarray analysis versus karyotyping for prenatally diagnosed ventriculomegaly by primary routine ultrasonography in a Chinese population.

Patients and methods

Patients and sampling

This retrospective study enrolled consecutive female patients that had been ultrasonographically diagnosed with intrauterine ventriculomegaly between 10–41 weeks of gestation and that were referred to Guangxi Zhuang Autonomous Region Maternal and Child Health Hospital, Nanning, Guangxi, China between November 2009 and May 2017. The hospital has an annual routine ultrasonographic screening rate of approximately 70 000.

According to the standard measurement of ventricular atrium width,[5] three specialists (J.L.Y., D.H.M. and J.Y.) in obstetric ultrasonography confirmed the presence of fetal ventriculomegaly. A proportion of women with a confirmed diagnosis were offered fetal karyotyping and infection screening to detect toxoplasmosis and cytomegalovirus. Microarray analysis was performed in a smaller group of women, with some women having both tests undertaken. Chorionic villus sampling was undertaken in the usual manner or amniotic fluid from women undergoing amniocentesis was submitted to the laboratory for karyotype analysis. The laboratory established cultures required for cytogenetic analysis. A sample of 7–10 ml of amniotic fluid or $\geq$2 mg of chorionic villus tissue was sent together with peripheral blood samples from each parent for microarray analysis. The inclusion criteria were: (i) advanced maternal age; (ii) structural anomalies detected on ultrasonography.

The study was approved by the Ethical Review Board of the Faculty of Medicine, Guangxi Zhuang Autonomous Region Maternal and Child Health Hospital (no. S201309-04). All patients that provided samples provided written informed consent.

Microarray analysis of CNVs

DNA was extracted from the tissue samples using a FlexiGene AGF3000 DNA kit (Qiagen, Hilden, Germany). The DNA was tested for contamination with maternal DNA using the AmpFLSTR™ Identifiler™ PCR Amplification Kit and a 3500xl capillary electrophoresis genetic analyser (both from Applied Biosystems, Carlsbad, CA, USA). Samples with > 10% maternal DNA contamination were excluded. Microarray assays were performed using an Affymetrix CytoScan™ array (Affymetrix, Santa Clara, CA, USA) for CNV analysis according to the manufacturer's protocol (supplied by Biosan Biochemical Technologies, Hangzhou, China). The microarray contains approximately 300 000 unique sequence probes with the resolution of 62–200 kb. Data were visualized with Chromosome Analysis Suite software version 2.1 (Affymetrix). Public databases were consulted to interpret the clinical significance for detected CNVs, including the Online Mendelian Inheritance in Man (OMIM) database,[9] Database of Chromosomal Imbalance and Phenotype in Humans using Ensembl Resources (DECIPHER),[10] ClinVar,[11] and Database of Genomic Variants (DGV).[12] CNVs were classified as pathogenic, likely benign, or variants of unknown significance (VOUS).[13]

Statistical analyses

All statistical analyses were performed using IBM SPSS Statistics for Windows, Version 19.0 (IBM Corp., Armonk, NY, USA). The mean ± SD were calculated for continuous data. Data were compared using χ^2-test or one-way analysis of variance. The 95% confidence intervals (CIs) for the prevalence rates were based on 10 000 bootstrap samples. A P-value < 0.05 was considered statistically significant and the Bonferroni correction was applied for multiple tests.

Results

This retrospective study identified 943 patients with suspected intrauterine ventriculomegaly, including 922 singleton and 21 twin pregnancies. Of the 943 cases, 880 women with a confirmed diagnosis of intrauterine ventriculomegaly were offered fetal karyotyping and infection screening to detect toxoplasmosis and cytomegalovirus, whereas microarray analysis was performed

on 114 patients. In total, 97 patients underwent both tests.

During the study period, 943 patients were identified with suspected cases of intrauterine ventriculomegaly that was diagnosed via ultrasonographic fetal anomaly screening among 520 000 registered pregnancies giving a prevalence of ventriculomegaly of 18.1 per 10 000 pregnancies (95% CI 6.0, 30.0). Among these 943 cases of ventriculomegaly, 21 (2.2%; 95% CI 1.3, 3.3) were twin pregnancies versus 922 (97.8%; 95% CI 96.7, 98.7) singleton pregnancies; 447 (47.4%; 95% CI 44.2, 50.7) unilateral ventriculomegaly versus 496 (52.6%; 95% CI 49.3, 55.8) bilateral ones; and 349 (37.0%, 95% CI 34.0, 40.0) isolated ventriculomegaly versus 594 (63.0%; 95% CI 60.0, 66.1) with additional prenatally identified complications (non-isolated ones). Overall, the proportions of mild, moderate, and severe cases were 81.4% (768 cases; 95% CI 79.0, 83.8), 9.1% (86 cases; 95% CI 7.2, 11.0), and 9.4% (89 cases; 95% CI 7.7, 11.3), respectively. Mean ± SD maternal age was 29.8 ± 5.1 years (range, 16–46 years), with a fetal male:female ratio (live births) of 2.1:1. The clinical characteristics of the study population are shown in Table 1. Non-isolated ventriculomegaly cases had significantly higher maternal age (29.6 ± 5.5 years) than isolated cases (27.9 ± 4.2 years; $P = 1.9 \times 10^{-6}$). The proportion of bilateral ventriculomegaly was increased in the non-isolated group (333 of 594; 56.1%) compared with the isolated group (163 of 349; 46.7%; $P = 0.005$), as well as severe ventriculomegaly (76 of 594 [12.8%] versus 13 of 349 [3.7%]; $P = 2.3 \times 10^{-5}$). There were 236 patients with missing pregnancy outcome data. The termination and caesarean rates were higher in the non-isolated group (171 of 460 [37.2%] and 126 of 280 [45.0%], respectively) than in the isolated group (31 of 247 [12.6%] and 62 of 215 [28.8%], respectively; both $P < 0.001$), whereas the live birth rate was significantly lower in the non-isolated group (280 of 460 [60.9%] versus 215 of 247 [87.0%]; $P = 1.6 \times 10^{-11}$).

Because the complications of twin pregnancy may relate to fetal ventriculomegaly,[14] only singleton cases were included for the subsequent assessment of fetal karyotyping and CNV screening. Microarray analysis was performed on 114 patients and the 63 abnormalities detected are listed in Table 2. The results of karyotyping and microarray analysis are shown in Table 3. Of the 922 singleton pregnancies, 880 cases were karyotyped with 108 (12.3%; 95% CI 10.1, 14.5) abnormal results, including 100 (11.4%; 95% CI 9.3, 13.4) autosomal, six (0.7%; 95% CI 0.2, 1.3) sex-chromosomal and two (0.2%; 95% CI 0.0, 0.6) triploidy abnormalities. Among these abnormalities, there were 54 (6.1%; 95% CI 4.7, 7.8) cases of autosomal trisomy. Meanwhile, 114 cases received microarray analysis with 63 (55.3%; 95% CI 47.4, 64.0) abnormal results, including 57 (50.0%; 95% CI 41.2, 59.6) autosomal, four (3.5%; 95% CI 0.9, 7.0) sex-chromosomal and two (1.8%; 95% CI 0.0, 4.4) triploidy abnormalities. There were 21 (18.4%; 95% CI 11.4, 26.3) cases of autosomal trisomy identified by microarray analysis. In addition, VOUS were detected in 21 (18.4%; 95% CI 11.4, 26.3) cases.

There were 97 cases examined by both karyotyping and microarray analysis. The consistency analysis between the karyotyping and microarray analysis is shown in Table 4. All apparent chromosome abnormalities (35 of 97; 36.1%) identified by karyotyping were detected with the use of microarray analysis. Microarray analysis also reported genetic abnormalities in 20 (20.6%; 95% CI 13.4, 29.9) additional cases not detected by karyotyping. Of these additional 20 cases, 11 (11.3%; 95% CI 5.2, 18.6) reported genetic abnormalities of uncertain clinical significance. The performance was significantly

Table 1. Maternal and pregnancy characteristics of the women ($n = 943$) diagnosed with fetal ventriculomegaly by prenatal ultrasonography.

Characteristic	All cases $n = 943$	Isolated cases $n = 349$	Non-isolated cases $n = 594$	Statistical significance[a]
Maternal age, years	29.8 ± 5.1	27.9 ± 4.2	29.6 ± 5.5	$P = 1.9 \times 10^{-6}$
Gestational age, weeks				
At first diagnosis	23.8 ± 8.2	24.3 ± 8.5	23.4 ± 8.1	NS
At delivery (live births)	37.0 ± 5.1	37.2 ± 4.9	36.6 ± 5.5	NS
Side, *n*, %, (95% CI)				$P = 0.005$
Unilateral	447, 47.4, (44.2, 50.7)	186, 53.3, (48.1, 58.5)	261, 43.9, (40.1, 48.3)	
Bilateral	496, 52.6, (49.3, 55.8)	163, 46.7, (41.5, 51.9)	333, 56.1, (51.7, 59.9)	
Atrium measurement, *n*, %, (95% CI)				$P = 2.3 \times 10^{-5}$
Mild, 10–12 mm	768, 81.4, (79.0, 83.9)	304, 87.1, (83.1, 90.5)	464, 78.1, (74.7, 81.5)	
Moderate, 13–15 mm	86, 9.1, (7.2, 11.0)	32, 9.2, (6.3, 12.3)	54, 9.1, (6.9, 11.4)	
Severe, $\geq$15 mm	89, 9.4, (7.7, 11.3)	13, 3.7, (2.0, 5.7)	76, 12.8, (10.1, 15.7)	
Pregnancy outcome, *n*, %, (95% CI)				
Missing data	236	102	134	$P = 1.6 \times 10^{-11}$
Late miscarriage	4, 0.6, (0.0, 1.1)	1, 0.4, (0.0, 1.2)	3, 0.7, (0.0, 1.5)	
Termination of pregnancy	202, 28.6, (25.3, 32.0)	31, 12.6, (8.5, 17.0)	171, 37.2, (32.8, 41.3)	
Stillbirth	6, 0.8, (0.3, 1.6)	–	6, 1.3, (0.4, 2.4)	
Live birth	495, 70.0, (66.5, 73.4)	215, 87.0, (82.6, 91.1)	280, 60.9, (56.5, 65.2)	
About live births, $n = 495$				
Model of delivery, *n*, %, (95% CI)				$P = 2.4 \times 10^{-4}$
Vaginal	307, 62.0, (57.6, 66.1)	153, 71.2, (64.7, 76.7)	154, 55.0, (49.3, 60.7)	
Caesarean	188, 38.0, (33.9, 42.4)	62, 28.8, (23.3, 35.3)	126, 45.0, (39.3, 50.7)	
Fetal sex ratio, male: female	2.1:1	2.1:1	2.1:1	NS
Birth weight, kg	3.2 ± 0.5	3.2 ± 0.4	3.1 ± 0.5	NS

Data presented as mean $\pm$ SD or *n* of patients, %, (95% confidence interval [CI]).

[a]Isolated group versus non-isolated ventriculomegaly group; χ^2-test or one-way analysis of variance; NS, no significant between-group difference ($P \geq 0.05$).

Table 2. Abnormalities detected by chromosomal microarray analysis ($n = 63$).

No.	Complications	Karyotyping	Microarray
1	Isolated	47,+21	arr(21)*3
2	Isolated	47,XN+21	arr(21)*3
3	Isolated	47,XX,+21	arr(21)*3
4	Isolated	45,X	arr(X)*1
5	Isolated	47,XXY,9qh+	arr(XXY)*1
6	Isolated	–	arr12*3
7	Isolated	–	arr14q22.150950067-52154846)*3
8	Isolated	–	arr1q21.1q21.2(146476526-149259380)*3
9	Isolated	–	arr2q12.3q13(108545409-110458666)*1
10	Isolated	–	arr4q28.1(127247924-127827145)*1
11	Isolated	–	arr4q35.2(189571541-190148795)*1
12	Isolated	–	chr1,2,3,5,7,8,10,11,17,19,20,22
13	Isolated	–	Xq11.2, Xq12, Xq21.2
14	Non-isolated	–	18p11.23
15	Non-isolated	46,XY,der(4)t(4;?18)(p16;q21)dn	4p16.1-16.3, 4p13.1-16.1
16	Non-isolated	69,XXX	arr(1-22)*3,XXX
17	Non-isolated	69,XXY	arr(1-22)*3,XXY
18	Non-isolated	–	arr(13)*3
19	Non-isolated	47,XN,+13	arr(13)*3
20	Non-isolated	47,XN,+18	arr(18)*3
21	Non-isolated	47,XN,+18	arr(18)*3
22	Non-isolated	47,XX,+18	arr(18)*3
23	Non-isolated	47,XX,+18	arr(18)*3
24	Non-isolated	47,+21	arr(21)*3
25	Non-isolated	47,+21	arr(21)*3
26	Non-isolated	47,+21	arr(21)*3
27	Non-isolated	47,XN,+21	arr(21)*3
28	Non-isolated	47,XN,+21	arr(21)*3
29	Non-isolated	47,XN,+21	arr(21)*3
30	Non-isolated	47,XN,+21	arr(21)*3
31	Non-isolated	47,XN,+21	arr(21)*3
32	Non-isolated	47,XN,+21	arr(21)*3
33	Non-isolated	47,XY,+21	arr(21)*3
34	Non-isolated	47,XY,+21	arr(21)*3
35	Non-isolated	47,XN,+8/46,XN	arr(8)*2-3
36	Non-isolated	47,XXY	arr(XXY)*1
37	Non-isolated	–	arr11p14.1p14.3(22348844-28989610)*1, arr21q11.2q21.3(14795475-27486796)*1
38	Non-isolated	47,+mar/46	arr12p13.33p11.1*3
39	Non-isolated	–	arr15q26.1q26.2(93682229-94632321)*1, arr19q13.43(56731478-59106242)*3
40	Non-isolated	–	arr16p11.2(29634212-30199805)*1
41	Non-isolated	–	arr16p13.3(209816-257548)*0
42	Non-isolated	–	arr16p13.3(223632-227379)*0
43	Non-isolated	45,-18/46,r(18)(p11q23)	arr18p11.32p11.31(12842-4946562)*1, arr18q22.3q23(71900332-78014582)*1

(continued)

Table 2. Continued.

No.	Complications	Karyotyping	Microarray
44	Non-isolated	–	arr1p36.33p36.22(752566-10473196)*1
45	Non-isolated	–	arr1p36.33p36.31(791,853-7,041,175)*1
46	Non-isolated	–	arr20p12.1(14745223-15422629)*1
47	Non-isolated	–	arr2p25.3pter(72184-1992624)x3, arr17p13.3pter(18901-728030)x1
48	Non-isolated	46,del(3)(q24q26.1)	arr3q24q26.1(144242847-165502724)*1
49	Non-isolated	46,XX,der(4)t(4;17)(q34;q24)	arr4q34.3q35.2(179769492-190880409)*1, 17q24.2q25.3(67031457-81047565)*3
50	Non-isolated	46,XN,del(5)(p14)	arr5p15.33p14.3(464153-23132422)*1
51	Non-isolated	–	arr5p15.33p15.1(354051-17484038)*1, arr5q34q35.3(165731079-180705539)*3
52	Non-isolated	–	arr5q23.1q31.1(119399177-135327491)*2
53	Non-isolated	–	arr5q35.2q35.3(175279492-180645207)*1
54	Non-isolated	–	arr5q35.2q35.3(176498882-178712059)*1
55	Non-isolated	–	arr7p22.1(4790971-6467451)*3
56	Non-isolated	–	arr7q11.1q11.21(61074194-63040655)*3
57	Non-isolated	–	arr7q21.1(23539563-24904315)*3, arr15q13.2(23539563-24904315)*1
58	Non-isolated	46,der(7)t(7;7)(p22;q21)	arr7q21.13q36.3(89859977-159119486)*3
59	Non-isolated	–	arr8q11.21q11.23(51519246-52910266)*3
60	Non-isolated	46,XN,del(9)(q21.3q22.3), ins(9)(q21.3q31.1q33.2)	arr9q21.32*1, arr9q31.1*3
61	Non-isolated	–	c.1543C>T(p.R485X)
62	Non-isolated	–	FGFR3 c.1138G>A(p.G380r)
63	Non-isolated	–	SURF: E7751C>T, 751 + 1G>A

Table 3. Results of the karyotyping and microarray analysis.

Variables	Karyotyping, $n = 880$	Microarray, $n = 114$
Abnormality	108, 12.3, (10.1, 14.5)	63, 55.3, (47.4, 64.0)
Autosome	100, 11.4, (9.3, 13.4)	57, 50.0, (41.2, 59.6)
Sex-chromosome	6, 0.7, (0.2, 1.3)	4, 3.5, (0.9, 7.0)
45,X	3, 0.3, (0.0, 0.8)	2, 1.8, (0.0, 4.4)
47,XXX; 47,XXY; 47,XYY	3, 0.3, (0.0, 0.8)	2, 1.8, (0.0, 4.4)
Triploidy (69,XXX; 69,XXY)	2, 0.2, (0.0, 0.6)	2, 1.8, (0.0, 4.4)
Autosomal trisomy	54, 6.1, (4.7, 7.8)	21, 18.4, (11.4, 26.3)
13	6, 0.7, (0.2, 1.3)	2, 1.8, (0.0, 4.4)
18	9, 1.0, (0.5, 1.8)	4, 3.5, (0.9, 7.0)
21	34, 3.9, (2.6, 5.2)	14, 12.3, (6.2, 18.4)
Others	5, 0.6, (0.1, 1.1)	1, 0.9, (0.0, 2.6)
Variant of unknown significance	–	21, 18.4, (11.4, 26.3)

Data presented as *n*, %, (95% confidence interval [CI]).

Table 4. Consistency analysis of karyotyping and microarray analysis in 97 samples.

Abnormality detection[α] Karyotyping	Microarray analysis	n, %, (95% confidence interval)
–	–	42, 43.3, (34.0, 53.6)
–	+	20, 20.6, (13.4, 29.9)
+	+	35, 36.1, (26.8, 45.4)
	Total	97

[α]Positive (+) and negative (–) results by karyotyping and microarray analysis.
Significant difference between karyotyping and microarray analysis (χ^2-test; $P = 2.4 \times 10^{-10}$).

different between karyotyping and microarray analysis ($P = 2.4 \times 10^{-10}$).

Discussion

This current retrospective study collected population-based data (2009–2017) of prenatally diagnosed fetal ventriculomegaly from a single clinical centre responsible for maternal and child health in the Guangxi Zhuang Autonomous Region. The centre annually receives approximately 70 000 pregnancies for routine prenatal ultrasonography. The prevalence of ventriculomegaly in this population was 18.1 per 10 000 pregnancies, which was much higher than the reported prevalence rate (approximately 11.5 per 10 000) in previous studies.[15,16] This is because approximately one-third of the patients were transferred from other regional maternal and child health hospitals, increasing the prevalence of the abnormality.

All ventriculomegaly cases were identified during the primary ultrasonographic scan at a mean gestational age of approximately 24 weeks, consistent with a previous report.[17] Ventriculomegaly was more often accompanied by additional complications (non-isolated 63.0%) and mild (81.4%) in this current population. As reported, fetuses with isolated mild (10–12 mm) ventriculomegaly are most likely to survive with normal neurodevelopment (>90%).[18,19] Notably in this current study, due to the large proportion of mild fetal ventriculomegaly, 70% of the cases delivered live births, and the children's information should be continuously followed-up to be referred for clinical consultation. This current study found non-isolated ventriculomegaly associated with higher maternal age (approximately 30 years) and high risks of bilateral (56.1%) and severe (12.8%) ventriculomegaly; 117 (37.2%) cases terminated the pregnancy. This current study confirms the risks in women with advanced maternal age.

This current study separately reviewed karyotype and microarray analysis. Karyotyping identified 12.3% of cases with chromosomal anomalies, whereas microarray analysis reported 55.3% abnormal results. Although the sample size for microarray analysis ($n = 114$) was too small to draw any final conclusions, these current results indicate that microarray analysis is equivalent to standard karyotype analysis for prenatal diagnosis and improves the detection of clinically relevant findings. Besides identification of fetuses with trisomy 8, 13, 18, 21, a sex chromosome aneuploidy, or triploidy,[4,20] rearrangements of 1p36,[21,22] 1q21.1, 7q11, 16p11.2, 16p13.3,[1,23] and other *de novo* mutations were also detected. All the detected rearrangements in this current study were considered to be disease-related alterations that cannot be completely excluded during genetic counselling. Microarray analysis provided additional clinically relevant information in 9.3% (9 of 97) of pregnancies

with standard indications for prenatal ventriculomegaly diagnosis. Meanwhile, uncertain genetic findings reported by microarray analysis occurred in 11.3% (11 of 97) of cases in which the karyotyping results were normal. Chromosomal microarray analysis is an efficient tool, significantly increasing the diagnostic power for prenatal diagnosis of early-onset fetal anomalies.[24–26] However, the detection of uncertain variants presents a challenge for counselling and causes parental anxiety, requiring continuous follow-up of neonates.

In conclusion, the results of this current study suggest that chromosomal microarray analysis used as a standard part of prenatal testing corresponded with the karyotyping results.

Declaration of conflicting interest

The authors declare that there are no conflicts of interest.

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