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Research Article

IUGR is Commonly Observed among Prenatally Diagnosed Chromosome 4p Deletion Syndrome

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Abstract

Objective: our study aimed at retrospectively assessing the abnormal prenatal ultrasound findings of chromosome 4p deletion syndrome.

Methods: 21 cases with abnormal sonographic signs revealed 4p deletion by Chromosome Microarray (CMA) in this retrospective analysis. Clinical information and molecular basis of this cohort were compared with those from other two groups in China, the critical region related to special ultrasound findings was mapped with the smallest regions of overlap.

Results: This is the largest prenatal series to evaluate the prenatal ultrasound features of 4p deletion syndrome detected by CMA. Firstly we refined the relationship between the genomic coordinates with IUGR in chromosome 4p terminal deletion syndrome. Additional chromosomal abnormalities was identified in 12 cases. Intrauterine embryonic arrest was diagnosed at first trimester for 9 cases. The most consistent ultrasound indicator was IUGR (95.5%), and the smallest region response for IUGR correspond to a 2.05Mb at 4p16.3-pter (chr4: 68,345-2,121,057, hg19). Increased Nuchal Translucency (NT) could be a risk factor for predicting WHS at first-trimester pregnancy with the rate of 16.6% from our data. A 3.6Mb microdeletion located at 4p16.3-pter (chr4: 68,345-3,753,422, hg19) might be the candidate region associated with increased NT.

Conclusion: We identified IUGR as the most common feature in prenatal 4p terminal deletion and Wolf-Hirschhorn syndrome. The existence of additional CNVs may contribution to possible explanations for the clinical heterogeneity of this syndrome. Prenatal findings of IUGR, increased NT or early spontaneous abortion should warrant the diagnosis of 4p terminal deletion WHS.

Keywords: IUGR; Prenatal diagnosis; 4p deletion syndrome; Chromosome microarray

Introduction

Wolf-Hirschhorn Syndrome (WHS; OMIM#194190) is a well-known contiguous gene deletion syndrome caused by chromosome 4p terminal deletion, first reported by Wolf and Hirschhorn in 1965 [1,2]. The prevalence was reported as 1 in 50,000 to 1 in 20,000 world widely and the female to male ratio was estimated to be 2:1 [3-5]. Distinctive craniofacial features of WHS patients are characterized as "Greek warrior helmet", including the wide bridge of the nose continuing to the forehead, high anterior hairline with prominent glabella, widely spaced eyes, epicanthus, highly arched eyebrows, short philtrum, downturned corners of the mouth, micrognathia, poorly formed ears with pits/tags, and microcephaly. Major structural anomalies such as renal hypoplasia, cardiac malformations, fetal growth retardation, and increased Nuchal Translucency (NT) are also reported in some of the WHS fetuses [6,7].

About 55% of WHS is caused by an isolated 4p terminal deletion, and 40%-45% is due to an unbalanced translocation with a 4p deletion and a duplication of another chromosome. Such unbalanced translocations can be *de novo* or inherited from a parent-carrier of the balanced rearrangement. Other rare complex conditions include chromosome 4 ring, 4p deletion mosaicism, or a derivative chromosome 4 leading to 4p16.3 deletion [8]. Conventional karyotyping analysis can detect 50-60% of WHS cases with deletions larger than 5Mb. FISH analysis with WHSCR (WHS critical region) probe or Chromosomal Microarray (CMA) could detects more that 95% of deletions in WHS [9].

Two critical regions contributed the core phenotype of WHS, namely WHSCR and WHSCR2. The WHSCR was a 165 kb interval at 4p16.3, about 2Mb away from the chromosome 4 telomere [10], defined between the loci D4S166 and D4S3327 [10,11]. WHSCR2, partially overlaps with WHSCR [12], was mapped within a 300-600 kb region in 4p16.3, resides 1.9Mb from the terminal of the 4p, between loci D4S3327 and D4S98-D4S168 [5]. Information on genotype-phenotype correlation for WHS is limited.

Prenatal ultrasound provides the opportunity to diagnose WHS prenatally. However, specific ultrasound markers has not been established for WHS. The most consistent presentation was severe IUGR [6,7], other signs such as increased NT, prominent glabella, ocular hypertelorism, micrognathia, short philtrum, cleft lip/palate, cystic cerebral lesions, abnormal nasal bone or renal hypoplasia were previously reported in cases of WHS diagnosed prenatally [13,14]. As the implementation of chromosomal microarray using in both

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Figure 1: The summarization of isolated 4p deletion cases from the literatures and our cohort with genomic coordinations and ultrasound findings.

postnatal and prenatal diagnosis of WHS, the critical regions for specific WHS features could probably be refined. Herein, we identified 21 prenatal cases with chromosome 4p terminal deletion detected by SNP-microarray by our retrospective study, we evaluated the deletion coordinates through reviewing the literature to refine the critical regions for IUGR and increased NT thickness by smallest regions pf overlap, and help further delineated the genotype-phenotype correlation in WHS with the specific prenatal ultrasound signs.

Materials and Methods

Subjects

This was a retrospective study to assess the clinical details of prenatal cases with 4p deletions Indications for prenatal invasive testings, prenatal ultrasound findings, CMA results and pregnancy outcome of these cases were reviewed. Overall, a total of 26,179 pregnant women were referred to our laboratory for invasive prenatal diagnosis from January 2013 to August 2018. The indications for invasive prenatal diagnosis include: fetus with various ultrasound abnormalities, embryonic arrest, intrauterine growth restriction (Head circumference/Abdominal Circumference/Biparietal Diameter <-2SD), cleft lip/palate, cystic cerebral lesions, abnormal nasal bone or renal hypoplasia, increased NT (thickness >3 millimeters), positive Down syndrome screening test, positive NIPT, family history with recurrent spontaneous miscarriage. Twenty-one cases with 4p-deletions were recruited in this study.

Prenatal ultrasound detection

Fetal ultrasound anatomy scans were routinely performed for pregnant women by experienced sonographers using GE E8 ultrasound machines (General Electric Healthcare, US) in Maternal and Child Health Hospital of Guangxi Autonomous Region. Transabdominal ultrasound examination included a full structural survey, and NT was measured according to established guidelines during the gestational week 11th to 13th.

Molecular and cytogenetic analysis

Chorionic villi sampling, amniocentesis or cordocentesis was performed under ultrasound guidance after informed consent. Genomic DNA was extracted using QIAamp DNA Blood Mini Kit (Qiagen, Germany) according to the manufacturer's protocol. SNP microarray testing was performed using Illumina HumanCytoSNP-12 v2.1 BeadChip (Illumina, USA). The SNP data were collected and analyzed by Illumina Genome Studio and KaryoStudio software. The coordinates were shown according to the human (GRCh37/hg19) assembly. The genomic critical regions for WHS related ultrasound abnormalities was proposed as according to the smallest regions of overlap based on the previously reported prenatal WHS cases and our WHS cohort.

Results

A total of 21 prenatal cases with 4p deletion were identified in our cohort. All of them were diagnosed prenatally by CMA, and twelve of them cases were also detected by karyotyping. Their detailed information were listed in (Table 1). Nine cases (42%) were referred to the hospital for first trimester ultrasound test for suspected early spontaneous abortion, the median maternal age was 29 years old (23-44) and the median gestational age at prenatal diagnosis was 27 weeks (11-34). Case 1-3, 6-8, 13, 16, 18-19, 21 with additional pathogenic chromosome abnormalities. Two cases with an increased NT thickness (case 7, case 19) carried additional chromosome 7p terminal duplication. In total, 10 cases (47%) were observed to have abnormal fetal ultrasound findings at second trimester of pregnancy.

Deletion sizes ranged from 5Mb to 35Mb, and all included WHS critical regions WHSCR and WHSCR2 (Figure 1). Two cases (cases 5, 6) with sole 4p terminal deletion resulted in sporadic abortion in early pregnancy. The smallest region relating to IUGR was located in the

Table 1: Pathogenic copy number variants identified by CMA among our patients with chromosome 4p terminal deletion.

Case	Maternal age (years)	Gestation (weeks+ days)	Pregnancy history	SNP array(hg19)	Inheritance	G-band	Ultrasound finding	Pregnancy outcomes
1	29	NA	G2P0	arr4p16.3p16.1(48,283-7,142,868) x1, 14q31. 1q32.33(80,848,449-107,282,437) x3	Maternal, 46,XX,t(4;14) (p16.1;q31.1)	NA	EA	SA
2	26	NA	G2P0	arr4p16. 3p15.33(48,283-11,547,106) x1, 15q21. 3q26.3(56,821,025-102,397,836)x3	Maternal, 46,XX,t(4;15) (p16;q22)	NA	EA	SA
3	31	8+4	G1P0	arr4p15.3 1p16.3(48,283-18,787,232)x1, 4p1 5.1p15.31(18,789,372-27,878,240) x1~2, 4q34. 3q35.2(179,929,126-190,880,409) x1~2	NA	NA	EA	SA
4	34	8+2	G2P0	arr4p16.3p15.1(48,283 -28,544,298)x1	NA	NA	EA	SA
5	36	9+1	G2P1	arr4p15.3 3p16.3(48,283-12,707,180)x1	NA	NA	EA	SA
6	31	10+5	G2P1	arr4p16.3p15.1(48,283-34,323,177) x1, 4q31. 3q35.2(155,331,774-190,880,409) x1.	NA	NA	EA	SA
7	38	11+6	G3P1	arr4p16.3(48,283-3,804,286)x1, 7p22.3p22.1(46,239-6,779,270)x3	NA	NA	NT: 3.8mm	SA
8	28	12+1	G4P0	arr4p16.3p16.1(48,283-8,728,783) x1, 4q35.2(188,609,718-190,880,409)x1, 10q11.2 2q11.23(46,947,635-51,739,867)x1, 8p23.3p23.1(176,818-11,898,209) x3	NA	NA	EA	SA
9	23	8+1	G0P0	arr4p15.1p16.3(48,283-34,573,079) x1	NA	NA	EA	SA
10	28	22+6	G1P1	arr4p16.3p15.2(48,283-25,065,147) x1	NA	46,XN,del(4)(p15)	IUGR,VSD,CDH	TOP
11	30	23+1	G2P1	arr4p16.3p15.2(48,283-22,878,904) x1	*de novo*	46,XX,del(4)(p15)	IUGR	TOP
12	28	24+4	G2P0	arr4p16. 3p15.32(48283-15,315,490)x1	NA	46,XX,del(4)(p15)	IUGR,STC,HNB	TOP
13	27	25	G2P1	arr4p16.3p16.1(48,283 -8,728,783) x1,	NA	46,XY	FGR	TOP
				8p23.3p23.2(176,818-6,974,050)x3				
14	28	26+4	G2P0	arr4p16.3p15.2(48,283-27,534,917) x1	*de novo*	46,XX,del(4)(p15.2)	Cleft lip	TOP
15	23	28+2	G1P0	arr4p16.3p16.1(48,283-11,236,408) x1	NA	46,XX,del(4)(p16.1p16.3)	CAH, CPC, HNB,RH, SUA	TOP
16	28	30	G1P0	arr4p16.3p16.1(48,283-7,048,842) x1, arr4p16. 1p13(7,055,603-43,968,054)x3	*de novo*	46,XY,der(4)del(4)(p16)dup(4) (p13p16)	IUGR,Cleft lip,VB,RH	TOP
17	26	31+6	G1P0	arr4p16.3p16.1(48,283-7,782,434) x1	NA	46,XY,del(4)(p16)	IUGR	TOP
18	28	32	G1P0	arr4p16.3p15.1(48,283-34,397,464) x1, 21q11. 2q21.1(14,687,571-20,989,949)x1	*de novo*	45,XN,der(4)t(4;21)(p15;q21),-21	IUGR,RH, Microcephaly	TOP
19	32	12+2	G3P1	arr4p16.3(48,283-3,350,248)x1, 7p15.3p22.3(46,239-22,584,183)x3	Maternal 46,XX,t(4,7) (p16,p15)	46,XX,der(4)t(4,7)(p16,p15)	NT:4.1mm	TOP
20	35	24+3	G3P1	arr4p16.3(48,283-2,300,841)x1.	NA	normal	IUGR,VB	TOP
21	28	16+3	G2	arr4p16.3(63,781-3,809,371)x1, 11p15.5p15.4(215,049-3,381,999) x3	Maternal 46,XX.isht(4,11) (p16.3,p15)	NA	NA	TOP

IUGR: Intrauterine Growth Restriction; SA: Spontaneous Abortion; EA: Embryonic Arrest; CDH: Congenital Diaphragmatic Hernia; STC: Small Transparent Compartment; HNB: Hypoplastic Nasal Bone; CAH: Cerebellar Axillary Hypoplasia; CPC: Choroid Plexus Cysts; RH: Renal Hypoplasia; SUA: Single Umbilical Artery; VB: Ventricular Broaden; NT/INF: Nuchal translucency/Fold; NA: Not Available.

band 4p16.3, contained the WHSCR and WHSCR2, approximately 2.05Mb from the telomere, described by Zhen et al. (Figure 1). Increased NT/NF thickness was counted to 18.7% in the cases with pure 4p deletion and the region was narrowed down within a 3.6Mb interval in 4p16.3 (Figure 1).

Discussion

Our study provided the largest series of prenatal WHS cases to assess the relationship between ultrasound abnormalities and their molecular defects. The incidence of 4p deletion in our cohort was one in 1250 (21/26,179). Among them, 47.6% (10/21) of our cases had an isolated 4p terminal deletion, while 38.0% (8/21) of our cases had a *de novo* or familial inherited unbalanced rearrangement, characterized by a deletion of 4p and a partial trisomy of another chromosome as reported before [15,16]. Since most of the previously reported prenatal WHS cases were identified by conventional karyotyping with a 4p deletion larger than 5Mb, it is difficult to precisely refine the critical regions for specific ultrasound anomaly [1,2,10,11,13,14,17-24]. Refining with the two prenatal centers that include diagnosis of WHS with CMA as stated in supplemental Table S1, we are able

Table 2: Summary of the WHS fetuses with pure terminal 4p deletion from the literature compared to the cases in our cohort.

Prenatal Ultrasound Signs	Previously reported(n=61)[a]	Our group(n=21)	Total
Embryonic Arrest	Not mentioned	8/21 (36.3%)	8/21 (36.3%)
IUGR [b]	55/56 (98.5%)	10/12[c] (83.3%)	65/68 (95.5%)
Typical"Greek warrior helmet" facial appearance	10/40 (27.5%)	0/12	10/58 (17.2%)
prominent glabella	2	-	-
short philtrum	1	-	-
micrognathia	5	2	-
hypertelorism	6	-	-
flat profile	2	-	-
Renal hypoplasia	5/56 (8.9%)	3/12 (25.0%)	8/68 (11.7%)
Cardiac malformation	7/56 (12.5%)	1/12 (8.3%)	8/68 (11.7%)
Cleft lip and palate	3/56 (5.3%)	2/12 (16.6%)	5/68 (7.3%)
Increased NT/NF	11/56 (19.6%)	2/12 (16.6%)	13/68 (19.1%)
Absent/hypoplastic nasal bone	6/56 (10.7%)	2/12 (16.6%)	8/68 (11.7%)

[a]Data collected from Xing Y, et al. [6] and Zhen L, et al. [7].
[b]IUGR was defined as HC/AC/BPD<-2 standard deviation.
[c]8 cases in our cohort presented embryonic arrest, and cases 21 were diagnosed with WHS using non-invasive prenatal testing without other detail ultrasound signs, thus the denominator decreased from 21 to 12.

to include more cases to refine the genotype-phenotype correlation of prenatal WHS. Through our observation, the most consistent ultrasound sign of prenatal WHS cases was IUGR (95.5%) (Table 2). Using overlapping analyses of 4p terminal deletions, we concluded a smallest region spanned from 4p16.3 to the telomere including WHSCR and WHSCR2 of 2.05Mb in size to be associated with severe IUGR, described by Li zhen et al. [7]. Similarly, 4p16.3-4pter of about 3.6Mb in size (chr4: 68,345-3,753,422, hg19, case10) might be the candidate region associated with increased NT (Figure 1). Both regions echoed the findings reported by Li et al., Wright et al., Zollino et al. proposed the critical region known as WHSCR and WHSCR2 by smallest regions of overlap [5,10]. Through the same strategy, we first refined the smallest region account for the distinctive IUGR and increased NT in prenatal WHS in China based on the CMA results. Notably, the phenotypic spectrum of postnatal WHS cases were classified into three categories based on the deletion size: (1) individuals with a deletion smaller than 3.5Mb at 4p16-4pter usually present with mild phenotype; (2) individuals with a deletion between 5 and 18 Mb usually presents with classic WHS phenotype; (3) individuals with a deletion larger than 22Mb usually present with major malformations [12]. Variable expressivity of clinical features also indicated that WHS was a contiguous gene syndrome [3,25]. The postnatal classification may not apply for prenatally diagnosed cases, as the phenotype-genotype correlation had not been well established during the first and second trimester. Most cases of 4p terminal deletion in our cohort or in other reported cases only presented with IUGR. Embryonic arrest occurred at first-trimester pregnancy with 4pter deletion had not been described before, the rate was 42.8% (9/21) in our cohort. Three cases with isolated 4pter deletion, and the remaining 6 cases had additional pathogenic chromosomal abnormalities which may contribute the clinical outcome. CMA for case 6 identified a complex rearrangement with terminal 4p and 4q deletion simultaneously likely resulting from a chromosome 4 ring. However, karyotype was not available to confirm the findings. CMA of case 7 with spontaneous miscarriage showed a 4p16.3 deletion and a 7p22.3p22.1 duplication. This finding raised the suspicion of parental balanced translocation. However, couple refused further evaluation. Our findings supported that important gene or genes within 4p terminal region is potentially responsible to regulate embryonic development. CMA is not a routine practice for pregnancies with early embryonic arrest, our findings support that CMA should be performed to look for submicroscopic chromosomal abnormalities in these cases.

Increased NT (>3mm) or NF (>6mm) thickness was another risk factor for WHS at first-trimester pregnancy. The rate of increased NT in WHS cases was 16.6% (2/12) which is comparable to previous report of 19% [6]. Case 31 were diagnosed with WHS by non-invasive prenatal testing (NIPT) with a large chromosome 4p deletion in the first trimester. Accuracy of NIPT on the detection of microdeletion syndrome is determined by the size thus many cases of WHS with small deletion (<3-5 megabase) would be missed by NIPT. Also, due to the low prevalence of WHS in the population, clinical application of NIPT on WHS is limited by a low positive predictive value [26]. Based on the findings of our cohort and previous reports, NT assessment might be more useful in detecting WHS in the first trimester comparing to NIPT.

IUGR was the most common ultrasound finding in prenatal WHS cases. The previously reported rate was 98.2% (55/56) [6,7], compared with 83.3% (10/12) in our cohort . Generally, the IUGR was observed by ultrasound at second trimester fetal structure evaluations, even early at 16th gestational week. The IUGR could be also various degree? and severe (all measurements were below the third percentile) in cases at the third trimester [27]. In our cohort, 7 cases were diagnosed with IUGR less than one percentile. The size of chromosome 4p deletion does not necessarily correlate with the severity of IUGR. For example, case 18 presented with severe IUGR (below 1st centile) with the CMA findings of 2.05Mb microdeletion at 4p16.3. While case 11 presented with IUGR below 3rd centile had the chromosome findings of a much larger deletion of 15.2Mb at 4p16.3-

4p16.1. In our cohort, we demonstrated that structural anomaly of WHS such as renal hypoplasia, cardiac anomaly, cleft lip and palate could be detected prenatally by USG. Although typical WHS facial characteristics was previously reported to be detectable prenatally, it would be difficult in prenatal USG and depend on the sonographer to detect subtle facial features [6,7,22,25,28]. Our study and prenatal ultrasound findings reiterate the clinical utility of CMA for fetuses with structural anomaly.

Conclusion

We presented the largest prenatal series of WHS diagnosed by CMA. IUGR was the most common features in prenatal WHS cases and the smallest region of overlap on chromosome 4p relating to IUGR was approximately 2.05Mb in size, span 4p16.3 to the telomere including WHSCR1 and WHSCR2. Embryonic arrest could occur in the cases with 4p terminal deletion. We also proposed the smallest deletion region relating to increased NT may be a 3.6Mb interval at 4p16.3-4pter. The rate of increased NT/NF thickness in WHS cases was 16.6% from our own data, which showed that increased NT/NF thickness is a strong indicator for WHS diagnosis. Prenatal CMA should be considered for pregnancies with isolated or multiple anomaly such as renal hypoplasia, cardiac malformation, cleft lip and palate, skeletal anomalies, absent/hypoplastic nasal bone to look for WHS.

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