Original Research

Diagnostic Yield of Cytogenomic Abnormalities in Current Prenatal Diagnosis: A Retrospective Analysis in a Clinical Cytogenetics Laboratory

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Background: Chromosome microarray analysis has been the first-tier genetic testing for pediatric patients and an integrated testing for prenatal cases. Aims: The purpose of this study was to evaluate the diagnostic yield from current prenatal genetic clinics and to provide guidance for future improvement on prenatal diagnosis of cytogenomic abnormalities. Material and Methods: A retrospective analysis of abnormal findings from karyotyping and array comparative genomic hybridization (aCGH) analysis of amniotic fluid (AF) specimens and chorionic villi samples (CVS) during the 2012-2015 interval was performed. The diagnostic efficiency as determined by the relative frequencies (RF) of different types of cytogenomic abnormalities was compared between prenatal and pediatric case series. Result: Data retrieved from this four-year interval presented 341 AF and 656 CVS with an annual caseload of 249 cases and an abnormality detection rate (ADR) of 20.2%. A comparison with prenatal testing performed in the 2007-2009 interval noted a 57% reduction of annual caseload and a 67% increase in ADR. While the ADR for structural chromosomal abnormalities remained the same; it was estimated that 80% of the increased ADR resulted from improved detection of numerical chromosomal abnormalities and 20% were from submicroscopic genomic aberrations detected by aCGH analysis. The RF for numerical chromosome abnormalities, structural chromosomal abnormalities, microdeletion and microduplication syndromes, and other genomic aberrations were 83.5%, 9%, 3.5% and 4% for the prenatal cases and 8.5%. 9.7%, 37.5% and 44.3% for a pediatric case series, respectively. Similar frequency in the detection of structural chromosomal abnormalities and striking different frequencies in other types of abnormalities were noted. Conclusion: These results indicated that the current prenatal diagnosis is effective in detecting chromosomal abnormalities but has a limitation on detecting genomic aberrations. Better correlations of ultrasonagraphic fetal anomalies and maternal serum fetal DNA quantitation with genomic aberrations are needed to improve prenatal cytogenomic analysis.
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INTRODUCTION

Prenatal diagnosis of fetuses with severe genetic defects has been important for pregnant women to select proper preventive and treatment options. Several clinical indications including advance maternal age, abnormal ultrasound findings, abnormal maternal serum screening, and family history of genetic abnormalities have been routinely used to evaluate the risk of pregnancies with chromosomal abnormalities.[1,2] Recently, maternal serum cell-free fetal DNA sequencing (cffDNA-seq) has been a validated and effective non-invasive approach to access the common aneuploidies directly in fetal DNA and thus improved the screening accuracy significantly.[3-5] Based on the abnormal findings from these indications, evidence-based prenatal genetic counseling will be offered to high-risk pregnancies and invasive procedures using amniotic fluid (AF) specimens and chorionic villus samples (CVS) will be recommended for the diagnosis of fetal chromosomal abnormalities. This progress has significantly increased the diagnostic yields, reduced unnecessary invasive procedures, and relieved the parental anxiety in current prenatal diagnosis.[6,7]

Cytogenetic analyses using rapid fluorescence in situ hybridization (FISH) or multiplex ligation-dependent probe amplification (MLPA) screening for common aneuploidies and conventional Giemsa-band karyotyping have been the standard procedures for prenatal diagnosis of chromosomal abnormalities from AF and CVS.[2,8,9] In the past decade, genome-wide microarray analysis using either array comparative genomic hybridization (aCGH) or single

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nucleotide polymorphism (SNP) array has been validated and recommended as the first-tier genetic testing for pediatric patients with developmental delay, intellectual disabilities and multiple congenital anomalies.[10,11] Significantly improved diagnostic yield of pathogenic genomic aberrations from pediatric patients has prompted a rapid integration of this genomic analysis into prenatal diagnosis.[12-15] The prenatal application of aCGH on abnormal cases has been effective in defining the gene content and breakpoints for unbalanced chromosomal abnormalities and detecting cryptic genomic imbalances.[16-18] Opinion and guidelines for prenatal diagnosis using microarray analysis have been introduced by American College of Obstetricians and Gynecologists and American College of Medical Genetics and Genomics.[19,20]

Since 2012, non-invasive cffDNA-seq result as a clinical indication and aCGH as a diagnostic testing for prenatal cases have been introduced in Yale prenatal clinics. A retrospective analysis of prenatal cases for a four-year interval (2012-2015) revealed the diagnostic yield of cytogenomic abnormalities. The diagnostic efficiency as determined by the relative frequencies of different types of cytogenomic abnormalities was compared between prenatal and pediatric case series. The findings from this study provided guidance for future improvement on prenatal diagnosis of cytogenomic abnormalities.

METHODS

During the selected time interval, pregnancies suspected with chromosomal abnormalities by various clinical indications were offered prenatal genetic counseling and options of karyotyping, FISH and aCGH were provided. The decisions from the couples to elect a testing could be affected by the clinical indications, family history, parental anxiety, insurance coverage, and other social and culture factors. In general, the laboratory performed FISH using the AneuVysion probes (Abbott Inc. Des Plaines, IL) for rapid detection of common aneuploidies involving chromosomes X, Y, 13, 18 and 21. FISH tests using probes for known microdeletion and microduplication loci were also performed for a rapid screening or confirmatory. Karyotyping was routinely performed on cultured amniocytes from AF or cultured fibroblast cells from CVS for all prenatal cases. Microarray analysis was mainly performed on cases with strong clinical indications and preauthorized by the insurance. For oligonucleotide aCGH analysis, genomic DNA was extracted from cultured amniocytes or directly prepared villi cells using the Gentra Puregene Kit (Qiagen, Valencia, CA). The DNA concentration was measured by a NanoDrop spectrophotometer (Thermo Fisher Scientific, Inc., Waltham, MA) and high molecular weight DNA was verified by agarose gel electrophoresis. For each sample, 2 ug of genomic DNA was used following the manufacturer's protocol for the Agilent Human Genome CGH microarray 180K kit (180,000 70-mer oligonucleotides, Agilent Technologies, Inc., Santa Clara, CA). This aCGH procedure can achieve 99% sensitivity and 99% specificity using a sliding window of five to seven contiguous oligonucleotides, indicating an analytical resolution of 100-150 kilobase for the 180K platform.[10] The genomic coordinates for detected aberrations from this aCGH analysis were based on the February 2009 Assembly (GRCh37/hg19) of the UCSC Human Genome browser (http://genome.ucsc.edu/).

The spectrum of cytogenomic abnormalities was classified into two major categories: chromosomal abnormalities and submicroscopic genomic aberrations. The chromosomal abnormalities were further divided into two major types: 1) numerical chromosomal abnormalities including aneuploidies of all autosomes and sex chromosomes and polyploidies of entire genome, and 2) structural chromosomal abnormalities including unbalanced structural rearrangements (deletions, duplications, marker chromosomes, etc.) and apparently balanced rearrangements (reciprocal translocations, inversions, ring chromosomes, etc.). The submicroscopic genomic aberrations were further divided into two major types: 1) recurrent syndromic microdeletions and microduplications (also termed as genomic disorders and continuous gene syndromes), and 2) other cryptic interstitial and subtelomeric pathogenic copy number variants (pCNV). To evaluate the diagnostic yield for various types of abnormalities, abnormality detection rate (ADR) was calculated by the number of abnormal cases divided by the total number of cases. A comparison of annual caseload and ADR from prenatal testing between the current and a previous time interval was performed. To evaluate the diagnostic efficiency for the spectrum of cytogenomic abnormalities, relative frequency (RF) was determined by the number of abnormalities in each major type divided by the total number of abnormal cases. The RF of chromosomal abnormalities and genomic aberrations from the present prenatal cases was compared with that from a pediatric case series performed by this laboratory.[21]

RESULTS

Data retrieved from the laboratory's CytoAccess database during the time interval of 2012-2015 found 341 AF specimens and 656 CVS for a total of 997 cases.[22] Of the 341 AF specimens submitted for karyotyping, 216 cases (63%) were analyzed by aCGH, and 84 cases (25%) were also tested by FISH; of the 656 CVS for karyotyping, 405 cases (62%) were tested by aCGH, and 101 cases (15%) were also tested by FISH. Of the 341 AF and 656 CVS cases analyzed by karyotyping, the ADR for chromosomal abnormalities was 12.6% (43 cases) and 21.8% (143 cases), respectively. The types of chromosomal abnormalities from AF and CVS cases are summarized in **Table 1**. Combined data showed an ADR of 18.7% for chromosomal abnormalities; while 16.8% were for numerical chromosome abnormalities and 1.9% were for structural chromosomal abnormalities. The ADR for most commonly seen numerical chromosomal abnormalities like trisomy 21, trisomy 18, monosomy X, and trisomy 13 were 8.8%, 3.4%, 1.1%, and 0.8%, respectively. The ADR for unbalanced and balanced structural chromosomal abnormalities was 1% and 0.9%, respectively. It was noted that two cases of trisomy 13 and one case of trisomy 21 were a result from carriers of a Robertsonian translocation and three out of the nine balanced chromosomal structural abnormalities were a Robertsonian translocation. The recurrent

constitutional translocation t(11;22)(q23.3;q11.2) was noted in one case. A mosaic pattern for an extra isochromosome of 12p was detected in one AF specimen for the diagnosis of the Pallister-Kallian syndrome.

Table 1. Chromosomal Abnormalities Detected in AF and CVS Cases.

	Total	Numerical Chromosomal Abnormalities*								Structural Chromosomal Abnormalities		
	Cases	T21	T18	T13	45,X	47,XXY/XXX	3n	Other	Subtotal	Unbalanced	Balanced	Subtotal
AF	341	22	8	2	2	0	2	1	37	5	1	6
CVS	656	66	26	6	9	6	4	13	130	5	8	13
Total	997	88	34	8	11	6	6	14	167	10	9	19
%		8.8	3.4	0.8	1.1	0.6	0.6	1.4	**16.8**	1.0	0.9	**1.9**

*T21, T18 and T13 for trisomy 21, trisomy 18 and trisomy 13, respectively; 3n for triploidy.

Table 2. Genomic Aberrations Detected by aCGH.*

Specimen	Indications	Chr	Size (Mb)	Abn	Genomic Coordinates (hg19)	Interpretations	Parental
Microdel/dup syndromes							
AF	AMA-37	15q11.1q11.2	2.886	del	Chr15:20,190,548-23,076,420	OMIM#615656	dn
AF	Suspected fetal abn	16p13.11	1.677	del	Chr16:14,910,205-16,586,915	DD, seizure	pat
AF	AMA-38, NT-4.7mm, increased DS risk	16p13.11	1.705	del	Chr16:14,968,855-16,674,321	DD, seizure	mat
CVS	Risk for Angelman syndrome	17p12	1.33	del	Chr17:14,111,772-15,442,066	OMIM#162500	nt
AF	TOF	22q11.21	1.315	dup	Chr22:17,274,635-18,589,433	OMIM#608363	nt
AF	Suspected fetal abn	22q11.21	2.844	del	Chr22:18,661,724-21,505,417	OMIM#188400	nt
AF	Incresed DS risk	Xq28	0.442	dup	ChrX:154,118,643-154,560,375	OMIM#300815	mat
Pathogenic CNVs							
CVS	Fetal edema	2p16.3	0.236	del	Chr2:51,166,666-51,402,457	OMIM#614332	mat
AF	AMA-36	9q34.3	0.199	dup	Chr9:140,378,700-140,577,586	OMIM#610253	pat
CVS	Increased DS risk	12q24.13	0.229	dup	Chr12:112,713,491-112,942,507	OMIM#176876	mat
CVS	NT-4.7mm	16q23.1q24.3	11.773	dup	Chr16:78,344,905-90,118,285	ID, Speech delay	nt
CVS	Fetal limb abn	17p13.3	0.149	dep	Chr17:1,130,776-1,279,570	SHFM	nt
AF	TOF	22q11.21	0.359	del	Chr22:21,081,260-21,440,514	CHD, Microcephaly	nt
AF	AMA-36, fetal spinal bifida	Xp22.13	0.309	dup	ChrX:18,287,690-18,596,189	DD, Autism	nt
CVS	AMA-40	Xq11.1q12	3.464	dup	ChrX:62,021,965-65,488,540	likely pathogenic	nt
Mosaic chromosome abnormalities							
CVS	AMA-40	mos 8q dup	76.61	dup	Chr8:69,669,887-146,280,020	Probably CPM	nt
CVS	NT-4.1 mm, suspected fetal abn	mos trisomy 7	159.071	dup	Chr7:54,185-159,125,464	Probably CPM	nt

*Abbreviations: AMA, advanced maternal age; TOF, tetralogy of fallot; Chr, chromosome; abn, abnormality; NT, nuchal translucence; del, deletion; dup, duplication; DD, developmental delay; ID, intellectual disability; SHFM, split hand/foot malformations; CHD, congenital heart defect; CPM, confined placenta mosaicism; pat, paternal; mat; maternal; nt, not tested.

Table 3. Abnormality Detection Rate (ADR) and Relative Frequencies (RF) for Abnormalities in Prenatal and Pediatric Cases.*

	Total	**Abn**	**Annual**	Num Chr Abn			Struc Chr Abn			Microdel/dup			pCNVs		
	Cases	**Cases**	**Caseload**	No.	ADR	RF	No.	ADR	RF	No.	ADR	RF	No.	ADR	RF
Prenatal (2007-2009)	1726	209	575	176	10.2%	84.0%	33	1.9%	16.0%	nd			nd		
Pranatal (2012-2015)	997	201	249	167	16.8%	83.5%	19	1.9%	9.0%	7	0.7%	3.5%	8	0.8%	4.0%
Pediatric (2006-2011)	1354	176	225	15	8.5%	8.5%	17	1.3%	9.7%	66	4.9%	37.5%	78	5.8%	44.3%

* Num, numerical; Struc, structural; chr, chromosome; nd, not detected.

Of the 216 AF and 405 CVS cases analyzed by aCGH, 1.1% (seven cases) were detected with a recurrent microdeletion and microduplication syndrome, 1.3% (eight cases) had a pCNV, and 0.3% (two cases) had a mosaic abnormal pattern. The ADR for pathogenic genomic aberrations was 2.4% of prenatal cases analyzed by aCGH. The clinical indications, types of genomic aberrations, genomic coordinates, clinical interpretation, and parental origin of the detected genomic aberrations are summarized in **Table 2**. Interpretations of clinical phenotypes for microdeletions at 15q11.1q11.2, 16p13.11, 17p12, and 22q11.21 and microduplications at 22q11.21 and Xq28 as well as other pCNVs were based on entries in the Online Mendelian Inheritance in Man (OMIM) database, reports from PubMed and other clinical resources.[23] Follow-up parental studies were recommended and a complete study was done in seven cases. Parental origin was determined in six cases and a de novo deletion was noted in one case. In one case detected with a mosaic pattern for a segmental duplication of 8q, karyotyping on cultured villi cells found a normal male pattern and FISH test on directly prepared villi confirmed the mosaic pattern. A follow-up amniocentesis detected a normal male pattern by karyotyping and FISH.

These results indicated the mosaic pattern detected by aCGH was most likely confined to the placenta. The mosaic pattern of trisomy 7 detected in another case was limited to DNA extracted from the villi cells and was not seen in cultured villi cells by karyotyping and FISH. This result also suggested for confined placenta mosaicism (CPM). Additionally, variants of unknown significance (VOUS) were detected in 37 pregnancies (data not shown); follow-up parental study performed on 18 families defined parental origin in 17 pregnancies and a de novo VOUS in one fetus.

From these 997 AF and CVS cases analyzed by karyotyping and aCGH, the ADR and RF of the 201 abnormal cases (excluding the two mosaic abnormal cases likely to be CPM from CVS by aCGH) are shown in **Table 3**. The annual caseload was 249 cases and the ADR was 16.8% and 1.9% for numerical and structural chromosomal abnormalities, respectively, and 2.4% for genomic aberrations. From prenatal testing performed on AF and CVS in a three-year interval of 2007-2009, the annual caseload was 575 cases and the ADR for numerical and structural chromosomal abnormalities were 10.2% and 1.9%, respectively.[2] A comparison of ADR between the current and previous prenatal case series demonstrated an approximately 57% reduction in invasive procedures and a 67% increase in ADR. A significantly increased diagnostic yield from 10.2% to 16.8% for numerical chromosomal abnormalities but a similar diagnostic yield of about 2% for structural chromosomal abnormalities were noted. More specifically, the diagnostic yield of trisomy 21 was increased from 4.6% to 8.8%. It was estimated that 80% of the increased ADR resulted from improved detection of numerical chromosomal abnormalities and 20% were from submicroscopic genomic aberrations detected by aCGH analysis. The RF for numerical chromosomal abnormalities, structural chromosomal abnormalities, recurrent microdeletion/duplication syndromes, and other pCNVs were 83.5% (167/201), 9% (18/201), 3.5% (7/201) and 4% (8/201), respectively. The RF for genomic aberrations could be underestimated because only two third of prenatal cases were analyzed by aCGH. In a pediatric case series analyzed by aCGH in this laboratory during the 2006-2011 interval, the RF for numerical chromosomal abnormalities, structural chromosomal abnormalities, recurrent microdeletion /duplication syndromes, and other pCNV were 8.5%, 9.7%, 37.5%, and 44.3%, respectively.[21] The RF for current prenatal case series and the pediatric case series showed a similar portion for structural chromosomal abnormalities but striking differences for other types of abnormalities. These results indicated that the current prenatal genetic evaluation is effective in detecting numerical chromosomal abnormalities but could be underdiagnosed for many genomic imbalances.

DISCUSSION

Our experience demonstrated some challenges facing current prenatal diagnosis. These challenges include the interpretation of genomic aberrations, considerations of penetrance and expressivity, requirements of immediate follow-up parental studies, unexpected mosaic pattern, findings of VOUS, and integrated application of karyotyping, FISH and aCGH. The detected genomic CNVs range from well-known syndromic and pathogenic, likely pathogenic, unknown significance, likely benign, and known benign. An evidence-based approach has been proposed for the interpretation of genomic variants.[13] Follow-up parental study was offered to almost all couples with pathogenic genomic aberrations and VOUS. A complete parental study was done in about 50% of these cases. It was estimated that 85% (6/7) of genomic aberrations and 95% (16/17) of VOUS were determined with a maternal or a paternal origin. This information helped a thorough assessment of clinical features for carriers with a genomic aberration or a VOUS and thus provide better genetic counseling. Mosaic pattern detected by aCGH but not found in cultured cells by karyotyping had been reported in pediatric and prenatal cases.[24,25] For mosaic pattern detected in CVS, follow-up amniocentesis should be considered to rule out CPM and confirm a true fetal mosaicism. Balanced chromosomal rearrangements and Robertsonian translocation induced numerical chromosomal abnormalities were noted in over 1% (12/997) of total cases and 6% (12/201) of abnormal cases. Considered RF of 92.5% for chromosomal abnormalities and of 6% for balanced structural abnormalities in the current prenatal setting, karyotyping is still the primary genetic testing and rapid FISH testing for common aneuploidies is highly effective in reliving parental anxiety. A strategy for balancing laboratory findings, clinical utility and patient anxiety in prenatal diagnosis has been proposed.[26]

The major challenge for prenatal diagnosis is to increase the diagnostic yield of syndromic and pathogenic genomic aberrations for better prevention of birth defects. The introduction of non-invasive cffDNA-seq screening and the integration of aCGH in prenatal diagnosis have reduced the invasive procedures and increased diagnostic yield. A systematic review of the prenatal diagnostic yield of targeted and whole-genome aCGH recognized that aCGH detected 3.5% and 5.2% of additional genomic aberrations when using general referral indications and a high-risk referral indication of ultrasound-detected malformations, respectively. However, the different diagnostic yields from different aCGH platforms and VOUSs were included within those additional genomic aberrations.[27] Two parallel karyotype and aCGH analyses on 1000 and 3171 consecutive prenatal cases detected numerical or large segmental chromosome abnormalities in 1.2-2.5% of fetuses and pCNV in 0.9-1.1% of fetuses, and over 55% of pCNV had recognizable abnormal ultrasound findings.[28,29] More recent studies showed a diagnostic yield of 1.3%-2.2% for submicroscopic genomic aberrations.[30,31] The ADR of 2.4% from our prenatal cases was similar to findings from other studies in the literature. All these studies indicated that aCGH can contribute important new information and detect clinically significant submicroscopic genomic aberrations. However, a comparison of RF for various types of cytogenomic abnormalities between prenatal and pediatric case series suggested an underdiagnosis of microdeletion/duplication syndromes and other pCNVs in the current prenatal setting.

CONCLUSION

Two approaches have been explored to improve the diagnostic yield for submicroscopic genomic aberrations. Firstly, established associations between genomic aberrations and prenatal ultrasonic abnormal findings could be useful clinical indications in genetic counseling for further diagnostic testing. For example, ultrasonagraphic fetal anomalies such as heart defects, overgrowth or undergrowth, and limb defects were used as clinical indications for prenatal detection of DiGeorge syndrome, Jacobsen syndrome, Cri du Chat syndromes, split hand/foot malformations, and Simpson-Galobi-Bemhel syndrome.[6,8,17,18] Secondly, an improved SNP-based cffDNA-seq has been validated for the detection of common microdeletion/duplication syndromes and thus should be considered for the general pregnant population regardless of maternal age and other screening results.[32] Future development of direct genomic analysis on circulating fetal cells isolated from maternal blood will provide a non-invasive prenatal diagnosis.[4] The advance in more accurate ultrasonic examination of fetal anomalies and better non-invasive screening will further improve the prenatal diagnosis of genomic aberrations.

CONFLICT OF INTEREST

None.

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