Ultrasound Obstet Gynecol 2011; **37**: 6–14
Published online 30 November 2010 in Wiley Online Library (wileyonlinelibrary.com). **DOI:** 10.1002/uog.7754

Additional information from array comparative genomic hybridization technology over conventional karyotyping in prenatal diagnosis: a systematic review and meta-analysis

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KEYWORDS: array CGH; prenatal diagnosis; ultrasound abnormalities

ABSTRACT

Objective *Array comparative genomic hybridization (CGH) is transforming clinical cytogenetics with its ability to interrogate the human genome at increasingly high resolution. The aim of this study was to determine whether array CGH testing in the prenatal population provides diagnostic information over conventional karyotyping.*

Methods *MEDLINE (1970 to December 2009), EMBASE (1980 to December 2009) and CINAHL (1982 to December 2009) databases were searched electronically. Studies were selected if array CGH was used on prenatal samples or if array CGH was used on postnatal samples following termination of pregnancy for structural abnormalities that were detected on an ultrasound scan. Of the 135 potential articles, 10 were included in this systematic review and eight were included in the meta-analysis. The pooled rate of extra information detected by array CGH when the prenatal karyotype was normal was meta-analyzed using a random-effects model. The pooled rate of receiving an array CGH result of unknown significance was also meta-analyzed.*

Results *Array CGH detected 3.6% (95% CI, 1.5–8.5) additional genomic imbalances when conventional karyotyping was 'normal', regardless of referral indication. This increased to 5.2% (95% CI, 1.9–13.9) more than karyotyping when the referral indication was a structural malformation on ultrasound.*

Conclusions *There appears to be an increased detection rate of chromosomal imbalances, compared with conventional karyotyping, when array CGH techniques are employed in the prenatal population. However, some are copy number imbalances that are not clinically significant. This carries implications for prenatal counseling and maternal anxiety. Copyright © 2010 ISUOG. Published by John Wiley & Sons, Ltd.*

INTRODUCTION

Structural chromosomal anomalies are a major cause of perinatal morbidity and mortality[1–3]. Since the 1960s, full chromosome analysis has been the mainstay of diagnosing karyotypic abnormality. Despite improvements in cytogenetic resolution, karyotyping may only detect anomalies to a resolution of 5–10 Mb[4]. Array comparative genomic hybridization (CGH) has several advantages over conventional chromosome analysis. A high-resolution oligonucleotide array is capable of detecting changes to a resolution of 1 kb (smaller than the average gene), and customized arrays designed for prenatal diagnosis have been developed.

One of the current challenges of the application of CGH microarrays in the clinical setting is determining whether a copy number imbalance is *de novo* and likely to be causative, or inherited and likely to be benign. When analyzing array data in a clinical setting, clinical cytogeneticists categorize copy number variants (CNVs) into those that are likely to be 'benign', those that are likely to be 'pathogenic' and those of 'unknown clinical significance'. CNVs that overlap critical regions of established microdeletion or microduplication syndromes are likely to be pathogenic[5].

Prenatal fetal karyotyping is offered during a pregnancy because a screening test has indicated a 'high' risk that the fetus may have aneuploidy, because of a structural anomaly on ultrasound examination, because of

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Accepted: 19 July 2010

a family history of chromosomal abnormality or because of parental choice. Conventional chromosome analysis using G-banding will detect chromosome anomalies such as trisomies 21, 18 and 13, and monosomy X, along with many structural rearrangements. However, there are a small number of pregnancies in which conventional karyotyping is reassuring but uncertainties persist about the underlying etiology.

Studies have been published indicating that array technologies may detect previously 'undiagnosed' chromosome aberrations. These studies have also highlighted limitations to this technology, not least the identification of unknown CNVs that may increase parental anxiety and difficulties in counseling. As this technology will become increasingly important in prenatal diagnosis, we sought to systematically review the literature and describe the evidence that array CGH may offer diagnostic information over conventional karyotyping, and specifically the value of arrays, in addition to karyotyping, for fetuses found to have a structural abnormality following an ultrasound scan.

METHODS

Our systematic review followed a prospective protocol developed using widely recommended and comprehensive methodology[6].

Data sources

The search focused only on prenatal studies using microarray technology. A search strategy was developed based on existing advice for prevalence searches[7,8]. MEDLINE (1970 to December 2009), EMBASE (1980 to December 2009) and CINAHL (1982 to December 2009) databases were searched electronically. The search of MEDLINE and EMBASE captured citations containing the relevant MeSH keywords and word variants for 'microarray' and 'prenatal'. The following terms were used to describe microarrays: array comparative genomic hybridization, microarray and oligonucleotide array. Similarly, antenatal diagnostics, fetal diagnostics, prenatal and fetal were used to capture 'prenatal'. Bibliographies of relevant articles were manually searched to identify papers not captured by the electronic searches. Web of Science (1996–2009) was used to capture any gray literature. Experts were also contacted for completeness of the search (the authors of the papers Coppinger *et al.*[9] and Van den Veyver *et al.*[10]). There were no language restrictions in the search or selection of papers.

Eligibility criteria for selecting studies

Studies were selected in a two-stage process. Initially, all abstracts or titles in the electronic searches were scrutinized by two reviewers (S.H. and S.P.) and full manuscripts of potentially eligible citations were obtained. Differences were resolved by discussion. Unresolved disagreements were resolved by a third reviewer (A.C.). Studies were selected if array CGH or microarray had been used on prenatal specimens (analyzed either during pregnancy or after delivery). We also selected reports if the same technology had been used on postnatal specimens following termination of pregnancy for structural abnormalities detected on an ultrasound scan. Papers were excluded if the testing was performed postnatally and the indication for running the array had not been determined prenatally. Papers were also excluded if the array was performed on children or adults or if it was used for preimplantation genetic diagnosis or for the diagnostic investigation of recurrent miscarriages. Finally, papers were excluded if they used the CGH technique and not array CGH. Non-English studies were assessed by people with command of the relevant language if the title or abstract appeared to fit the criteria. Only papers that allowed generation of a 2×2 table (comparing karyotyping with array) were included. In two instances, in order to construct a 2×2 table the authors were contacted. In the case of Coppinger *et al.*[9], direct discussion/correspondence allowed extra information to be obtained and for us to include the paper. In the second case (Van den Veyver *et al.*[10]), we were still unable to include the paper because the authors were unable to provide us with enough information to complete a 2×2 table.

Data extraction

Data were extracted by two reviewers (S.H. and S.P.). For each of the outcomes, data were extracted into tables, giving descriptive and numerical information for each study. Data were extracted on study characteristics and data quality. Data were used to construct 2×2 tables of test accuracy comparing normal and abnormal karyotype results against normal and abnormal microarray results. Case studies of fewer than five cases were excluded from the meta-analysis.

Quality assessment

All articles meeting the selection criteria were assessed for quality using items from validated tools (Figure 1). A study was considered to be of good quality if it used a prospective design, if it used a representative population (i.e. it used array technology on all samples, not just on those with an exclusively normal or abnormal conventional karyotype), if it performed array testing on parents to aid interpretation of CNVs and if it used a validated assessment tool (i.e. an identifiable, reproducible array). Expert opinion from cytogeneticists (D.M. and E.V.D.) at the West Midlands Regional Genetics Department was sought to determine the validity of the array used.

Data synthesis

The analysis was performed in two steps depending on the way in which the CNVs were grouped. The first

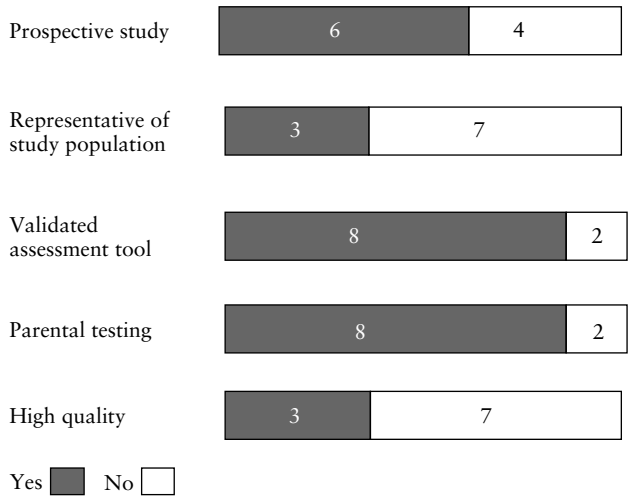

Figure 1 Quality assessment of the 10 papers included in the systematic review.

analysis grouped pathogenic, unknown and benign CNVs as array-detectable variants. The second analysis moved benign CNVs into the normal group, leaving the abnormal CNVs as those that were pathogenic plus those that were of unknown significance and potentially pathogenic. Analysis was performed for samples undergoing both karyotyping and array, regardless of the clinical indication (maternal anxiety, high risk on screening serum for Down syndrome and/or structural abnormality on ultrasound scan). Analysis was then performed for those undergoing chromosomal analysis because of a structural abnormality found during an ultrasound scan.

We explored the possibility of separating the data further by attempting to compare different sample types (e.g. from amniocentesis and chorionic villus sampling) and the effect that this may have on the array CGH results. However, this was not possible because, with the exception of one paper[9], the studies did not record from which sample type the DNA was extracted when an abnormal chromosomal result was found.

Using 2×2 tables, we computed and pooled the percentage agreement between the two technologies (with 95% CI) for the articles overall. The calculated percentage of extra cases identified by array in those with a normal karyotype (both overall and by referral indication) with 95% CI was calculated and pooled. Finally, we calculated and pooled the percentage of cases in which a result of 'unknown significance' was reported. Heterogeneity in rates was examined graphically and statistically. For graphical assessment, Forest plots of point estimates of rates and their 95% CI were used. For exploration of reasons for heterogeneity, stratified analysis was performed according to the features of the population (indication for referral). For the meta-analysis, log rates were pooled, weighting each study by the inverse of its variance[11], and the summary estimates were exponentiated. A random-effects model was used in the light of heterogeneity. All statistical analyses were performed using Stata 8.0 statistical software (Stata Corp., College Station, TX, USA).

RESULTS

The process of literature identification and selection is summarized in Figure 2. There were 10 primary articles identified as meeting the selection criteria[9,12–20]. Of the original articles, 97 were excluded because they did not meet the selection criteria. The remaining 38 articles were obtained and reviewed, and a further eight articles were requested after reviewing the reference lists. Of these 46 articles, 36 were then excluded as they did not meet selection criteria. The 10 primary studies, containing 798 participants, met the inclusion criteria to be included in the systematic review[9,12–20]. Eight of these studies were included in the meta-analysis[9,12–14,17–20] and two were excluded from the meta-analysis because array CGH was only performed when an abnormal karyotype had been detected[15,16].

Table 1 summarizes the characteristics of the publications used, including the design of the study (retrospective or prospective), the array type, sample type, if the array was targeted or covered the whole genome, the indication for the array (divided into different structural abnormalities where known) and the sample size. Study quality

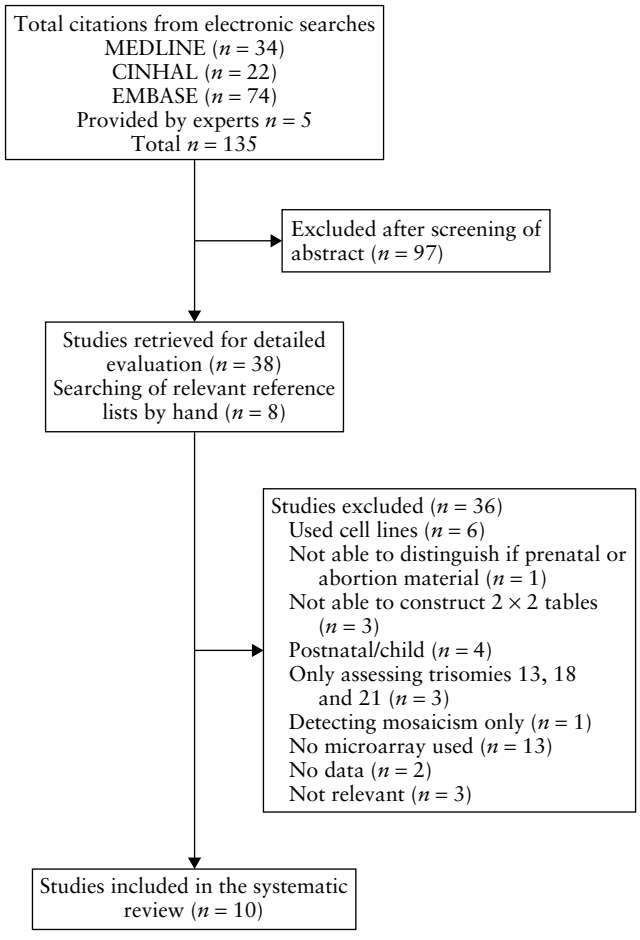

Figure 2 Selection process of the 10 papers included in the systematic review.

assessment showed deficiencies in many areas of methods (Figure 1). Only three papers met all four quality criteria: being prospective in design; using array and karyotyping on a representative population (i.e. the population did not have all known abnormal/normal karyotypes); investigating parents to aid interpretation of CNVs; and using a validated assessment tool[12,13,20].

The overall agreement between karyotype and array results was 88.2% (95% CI, 79.2–98.2). When benign CNVs were removed from the abnormal array group and treated as normal array results (as described above in the second analysis) the agreement was increased, to 95.6% (95% CI, 86–100%). The data were homogeneous ($P = 0.99$ and $P = 0.97$, respectively). Four out of 10 papers were used to review the overall agreement between karyotype results and array results ($n = 333$). Six out of 10 papers[14–19] could not be included because the dataset was not complete (i.e. the sample population was skewed by only using arrays on those samples with all normal or all abnormal karyotypes).

Array CGH detected 12% (95% CI, 8.8–16.4%) more chromosomal imbalances overall when karyotyping was 'normal' (Figure 3a) when the array was performed for any clinical indication. When benign CNVs were recognized, removed and treated as normal results, the detection rate decreased to 3.6% (95% CI, 1.5–8.5%) (Figure 3b). This 3.6% included all CNVs known to be pathogenic and those of unknown significance with the potential to be pathogenic. We therefore calculated how often a result of unknown significance would be found when array CGH was performed prenatally for any clinical indication. Results of 'unknown significance' were found in 1.1% (95% CI, 0.4–2.7%) of cases. Eight out of 10 papers were used for these meta-analyses[9,12–14,17–20] ($n = 751$). Two were excluded because they did not contain data for chromosomal anomaly detection rate by array when a normal karyotype was reported[15,16]. The paper by Sahoo *et al.*[12] was included in the analysis as having three results of unknown significance; the table of results in this paper (Table 1) implies that one of these (Case 3) was probably benign, but the text describes how the parents were 'counseled as to the unknown significance of the results' and it is therefore included as a result of unknown significance. These data were heterogeneous.

One of the papers appeared to contribute disproportionately to the heterogeneity of the data[18]. This paper used a higher resolution array (Affymetrix SNP 6) and did not use parental testing for clarification of CNVs of unknown significance. It therefore had a high detection rate of all CNVs: pathological, unknown significance and benign. Therefore, we performed a sensitivity analysis by excluding the results from this paper. With this paper excluded, the array detected 10.7% (95% CI, 9.1–12.6) more chromosomal imbalances when karyotyping was normal compared with 12% (95% CI, 8.8–16.4%) with the results of this paper included. With exclusion of the paper by Tyreman *et al.*[18], and when benign CNVs were removed and treated as normal results (analysis 2), the detection rate of chromosomal imbalances by array CGH decreased from 3.6% to 2.9% (95% CI, 1.3–6.3) when karyotyping was normal. Exclusion of this paper did not significantly reduce the array CGH detection rate; in addition, the data were still heterogeneous. Taking this into account, and given that the paper by Tyreman *et al.*[18] is an important paper with one of the largest cohorts of patients, we feel that its inclusion is important to present the totality of evidence.

Conventional karyotyping did not detect any chromosomal imbalances that were not detected by array CGH in the same eight papers used in the meta-analysis described above. Two papers included in the systematic review[15,16], but not in the meta-analysis, used array CGH only when an abnormal karyotype had been found. They found that array CGH was not able to detect one case of triploidy and 14 cases of balanced translocation. These two papers were not included in the meta-analysis because they only studied cases with abnormal karyotype results and therefore a 2×2 table of their results could not be formed.

Results in cases when a structural abnormality was noted on ultrasound scan

Array technology detected overall 11.2% (95% CI, 5.7–22.1) more chromosomal imbalances above that of conventional karyotyping (Figure 3a). When 'benign CNVs' were removed from the analysis and placed with the normal array results, the detection rate of chromosomal abnormalities decreased to 5.2% (95% CI, 1.9–13.9); this included results that are known to be pathological, and those of unknown significance with the potential to be pathological (Figure 3b). Six papers were used[13,14,17–20]. These papers all contained results on patients who had undergone karyotyping and array tests because they had pregnancies where a structural fetal malformation was suspected on ultrasound scanning ($n = 359$). The size of these chromosomal imbalances ranged, depending on the resolution of the array CGH used, from 60 kb[18] to 60 Mb[17]. In 1.9% (95% CI, 0.4–9.5) of cases where the patient was referred because of a fetal anomaly on an ultrasound scan and where conventional karyotyping was 'normal', a result of 'unknown significance' was reported. These data were heterogeneous ($P < 0.0001$).

The actual numbers of different structural abnormalities were recorded in four out of the six papers[9,14,18,19]. Where possible, the different structural abnormalities are recorded in Table 1. The pooled data from the four papers show that the largest numbers of patients had cardiac abnormalities ($n = 88$), increased nuchal translucencies, cystic hygromata or hydrops ($n = 82$), or central nervous system abnormalities ($n = 60$). It was not possible to divide the structural abnormalities into groups to perform separate analysis for array CGH testing because all four papers included groups with either 'multiple congenital

Table 1 Characteristics of the studies included

Reference/ study design	*Array type*	*Probe*	*Genome (WG/TG)*	*Sample type*	*Indication for array*	*Sample size (n)*
Coppinger *et al.* (2009)[9] Prospective	Signature prenatal chip V 4.0, commercial	> 2100 BAC probes	TG	Amniotic fluid $n = 40$ CVS $n = 22$	Anxiety $n = 6$ Family history $n = 19$ Advanced maternal age $n = 3$ Abnormal maternal serum screen $n = 1$ Abnormal ultrasound $n = 33$ (CNS $n = 3$; skeletal $n = 1$; CH/NT/hydrops $n = 18$; GI $n = 1$; IUGR $n = 1$; MCA $n = 7$; unspecified $n = 7$) All normal karyotype $n = 62$	62
	Signature chip whole genome, commercial	4670 BAC probes	WG	Amniotic fluid $n = 149$ CVS $n = 30$ Unspecified prenatal cell type $n = 3$	Anxiety $n = 3$ Family history $n = 17$ Advanced maternal age $n = 5$ Abnormal maternal serum screen $n = 2$ Abnormal ultrasound $n = 155$ (CNS $n = 16$; musculoskeletal $n = 8$; cleft lip $n = 6$; CH/NT/hydrops $n = 24$; GI $n = 4$; renal/ambiguous genitalia $n = 4$; cardiac $n = 13$; IUGR $n = 7$; MCA $n = 63$; unspecified $n = 10$)	182
Kleeman *et al.* (2009)[19] Prospective	Signature prenatal chip V 4.0, commercial, 26 patients	1887 BAC probes	TG	Amniotic fluid $n = 47$	Abnormal ultrasound scan and normal karyotyping $n = 50$ (cardiac $n = 24$; CNS $n = 6$; skeletal $n = 6$; urogenital $n = 4$; cleft lip/palate $n = 2$; CH/NT/hydrops $n = 3$; GI $n = 2$; multiple $n = 17$; growth disorder $n = 3$)	50
	Signature whole-genome chip, commercial	4685 BAC probes	WG	CVS $n = 3$		
Tyreman *et al.* (2009)[18] Retrospective	Genechip SNP 6.0 array (Affymetrrix), commercial	946 000 probes (CNVs)	WG	Amniotic fluid $n = 87$ CVS $n = 15$ Placenta biopsy following termination of pregnancy $n = 4$	Ultrasound anomaly $n = 106$ (cardiac $n = 34$; multisystem $n = 24$; large NT/hydrops/CH $n = 18$; CNS $n = 16$; skeletal $n = 6$; abdominal wall $n = 2$; others $n = 6$)	106
Bi *et al.* (2008)[13] Prospective	BCM V6 Oligonucleotide array (V6 Oligo) (Agilent), commercial	44 000 oligonucleotide probes	WG and TG	Amniotic fluid	Maternal age $n = 6$ Anomaly on ultrasound $n = 5$ Family history abnormality $n = 2$ Multiple miscarriages $n = 1$	14 pregnancies 15 fetuses

Table 1 (*Continued*)

Reference/ study design	*Array type*	*Probe*	*Genome (WG/TG)*	*Sample type*	*Indication for array*	*Sample Size* (n)
Shaffer *et al.* (2008)[14] Prospective	Prenatal BAC array version (signature), commercial	2100 BAC probes	TG	Prenatal cultured amniotic fluid or CVS; postnatal blood	Family history $n = 19$ Maternal age $n = 2$ Parental anxiety $n = 20$ Anomaly on ultrasound $n = 110$ (abnormal genitalia $n = 6$; CNS $n = 19$; CH/NF/NT/hydrops $n = 22$; GI $n = 9$; dysmorphic $n = 4$; cardiac $n = 17$; IUGR $n = 2$; multiple $n = 3$; micrognathia $n = 2$; midline defect $n = 8$; renal $n = 2$; skeletal $n = 11$; SUA $n = 1$; others $n = 4$)	151
Vialard *et al.* (2008)[20] Prospective	Genosensor BAC/PAC array 300 (Vysis/Abbott), commercial	287 BAC probes	TG	Muscle biopsy $n = 15$; lung biopsy $n = 13$; thymus $n = 4$; skin $n = 3$; liver $n = 3$; bladder $n = 1$	Two or more abnormalities cardiovascular/urogenital/ skeletal/digestive/CNS	39
De Gregori *et al.* (2007)[16] Retrospective	60-mer oligonucleotide microarray, commercial	60-mer oligonucleotide probes	WG	Not stated	Reciprocal translocations $n = 14$ Maternal age $n = 3$	17
Rickman *et al.* (2006)[15] Retrospective	BAC/PAC resolution 10 Mb, common microdeletion syndrome, own array	600 BAC probes	TG	Cultured amniocytes or CVS	Previously known karyotypes All known unbalanced rearrangements	30
Sahoo *et al.* (2006)[12] Prospective	BCM v4.0, Baylor, commercial	366 BAC probes	TG	Amniotic fluid $n = 56$ (26 uncultured) CVS $n = 42$ (32 uncultured)	Increased maternal age Increased serum screen Family history Abnormality on ultrasound	98
Le Caignec *et al.* (2005)[17] Retrospective	Genosensor BAC/PAC array 300 (Vysis/Abbott), commercial	287 BAC probes	TG	Frozen fetal tissue	All normal karyotype All had malformations All had at least three anomalies in CVS/urogenital/digestive/CNS	49

BAC, bacterial artificial chromosome; BCM, Baylor College of Medicine; CH, cystic hygroma; CNS, central nervous system; CNVs, copy number variants; CVS, chorionic villus sampling; GI, gastrointestinal; IUGR, intrauterine growth restriction; MCA, middle cerebral artery; NF, nuchal fold; NT, nuchal translucency; PAC, plasmid artificial chromosome; SNP, single nucleotide polymorphism; SUA, single umbilical artery; TG, targeted genome; WG, whole genome.

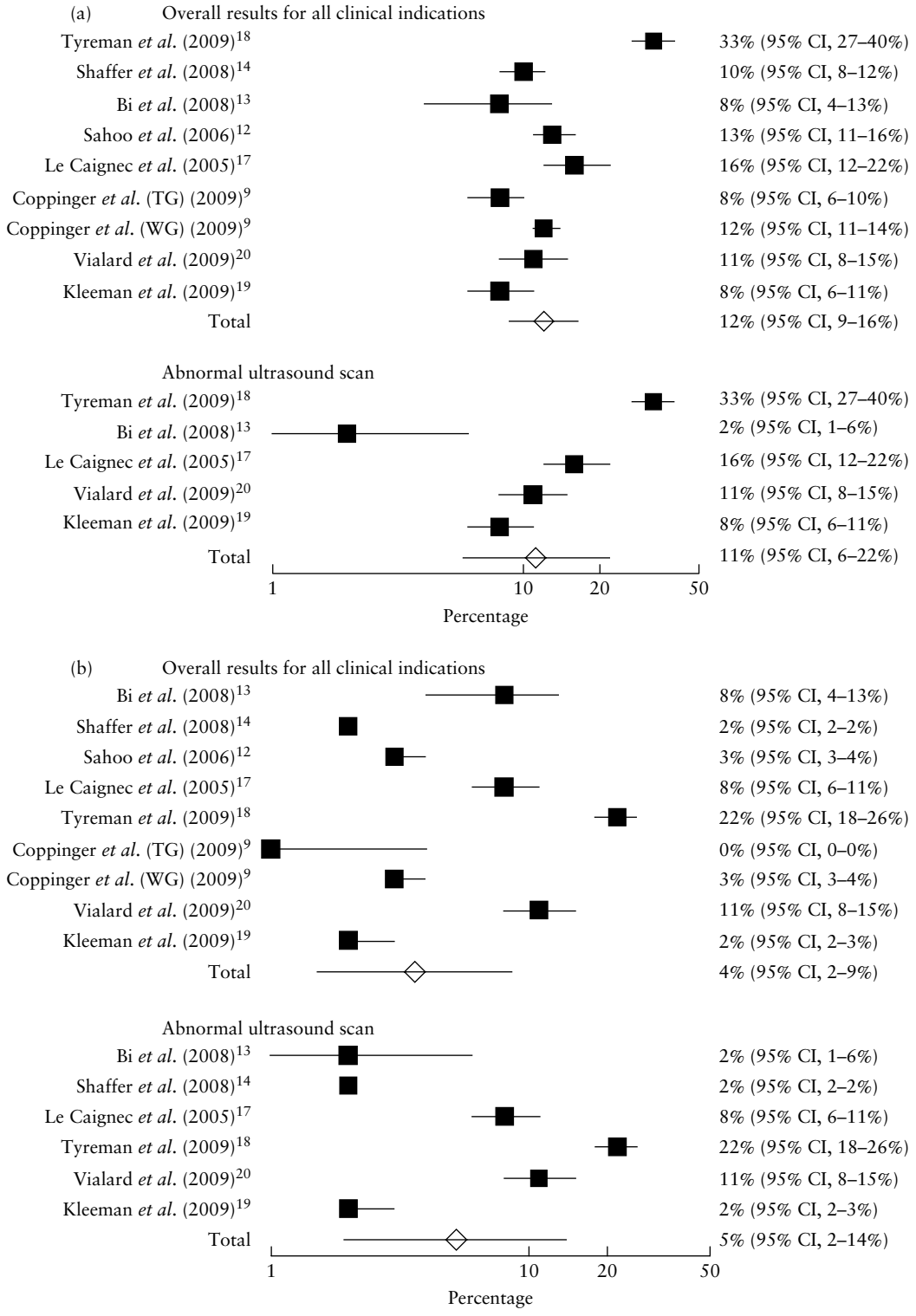

Figure 3 Forest Plot. Meta-analysis of the detection rate of chromosomal imbalances by array comparative genomic hybridization when karyotyping is normal and chromosomal testing is performed for either any clinical indication or an abnormal ultrasound scan. (a) Analysis 1: array results showing chromosomal imbalances that are copy number variants (CNVs) which are pathogenic, of unknown significance or benign. (b) Analysis 2: array results showing chromosomal differences that are CNVs which are pathogenic or of unknown significance. Benign CNVs were removed and treated as normal results. TG, targeted genome; WG, whole genome.

abnormalities', which was not broken down further, or 'other', where the abnormality was not specified. None of the papers included single 'soft' markers, although the paper by Tyreman *et al.* included multiple soft markers[18]. The vast majority were major abnormalities. The papers also did not always provide data postdelivery/postmortem so it was not possible in most cases to establish if the abnormality was confirmed or, in the case of increased nuchal translucency, if it was linked to other structural abnormalities.

Conventional karyotyping did not detect any chromosomal imbalances that were not detected also by array CGH.

DISCUSSION

Good overall agreement between prenatal array technology results and conventional cytogenetic karyotyping from data in the current literature was obtained, as expected. This increased further with the removal of 'benign' CNVs, identified by the examination of databases of DNA made available by collaborations such as the Wellcome Trust Case Control Consortium[21] or the Database of Genomic Variants (DGV)[22]. It is to be expected that the percentage agreement between technologies would increase with the removal of 'benign' CNVs because the remaining microarray results are more likely to be pathogenic.

Array CGH detected notably more chromosomal imbalances than conventional karyotyping, both when it was performed prenatally for any clinical indication and when it was performed for a structural abnormality detected during an ultrasound scan. As well as results of a known pathogenic nature, this also includes results of unknown pathogenic significance.

Although only occurring rarely, these results are of concern as they may both increase parental anxiety and lead to problems in prenatal counseling. The frequency of CNV of unknown significance is increased if parental samples are not available as analysis will reveal whether the variant detected in the fetus is familial or *de novo*. However, because of incomplete/variable penetrance, familial variants are not always benign[5].

Karyotyping did not detect any chromosomal imbalances when array CGH was reported as normal in those papers used in the meta-analysis[9,12–14,17–20]. This is reassuring because it suggests that array CGH alone will not miss many significant results, and that the areas in which microarray technology is weak (balanced translocations, inversions and a lower sensitivity for triploidy) are not common in a typical referral population.

The strength of the study lay in the rigor of the methodology. It met the quality criteria laid down in the MOOSE[23] statement. The meta-analysis contained a relatively small sample size of 751 participants for overall analysis and 409 participants with fetal anomalies identified using ultrasound. However, as many studies published in this area are single case studies, this would appear to be a fairly large cohort. Papers were heterogeneous, with both prospective and retrospective methodology, different indication for referral and different microarrays used. This accounts for the large CIs in our analysis. The inclusion of some published studies that include participants with a known normal karyotype may have influenced the results because they are not necessarily a representative population. Array technologies have increased in resolution since these studies were conducted and they have also become commercially available, allowing greater validation of results between different published studies. The authors cannot allow for ascertainment bias towards cases that clinicians may have felt would have yielded an abnormal result from array and therefore included them in the results. It is recognized that this is a developing scientific field and the literature on this topic is increasing with time. These data represent a critical appraisal of the literature to date and provide a summary for clinicians at the present time.

This systematic review provides evidence of the relative advantage of using array testing in prenatal diagnosis, even when the karyotype is normal. The additional detection of CNVs by array technologies is a combination of known pathological findings but also results of 'unknown significance'. With emerging array technologies of increasing resolution, the amount of CNVs that are uninterpretable will increase and be associated with increased parental anxiety. Up to 12% of any individual's genome is likely to exhibit normal copy number variation and there is emerging evidence of a huge degree of structural complexity within these chromosomal regions[24]. In addition, limited data exist on the prevalence of CNVs between different ethnic populations[25]. These concerns have led to recent recommendations from the American College of Obstetricians and Gynecologists (ACOG) that conventional karyotyping should remain the principal cytogenetic tool in prenatal diagnosis. ACOG has also suggested that targeted arrays can be offered as an adjunct in prenatal cases with abnormal anatomical findings and a normal conventional karyotype[26].

Conclusion

There appears to be an increased detection rate of chromosomal abnormalities with array CGH, both for prenatal indications overall and when congenital malformations were noted on ultrasound scans. However, the large CIs obtained in the analysis show that more work is required before we can answer the question of absolute detection rate over conventional karyotyping.

Further prospective research is needed in this area on a large cohort that has undergone both karyotyping and analysis using a commercial reproducible array. The optimum resolution of an array to be used in a prenatal setting has not yet been decided. A targeted array is suitable because of its ability to identify CNVs in known disease-specific loci of the human genome, but risks missing a pathogenic CNV that is absent in these particular genomic regions. A high-resolution array will have the ability to detect a greater number of CNVs but risks having more results of unknown certainty, which need additional time for interpretation and provoke additional uncertainty. Perhaps while this technology is being investigated, targeted arrays are more suitable.

Health economic assessment of microarrays is important when evaluating implementation of this prenatal diagnostic test in routine practice. At present within the UK National Health Service (NHS) setting, almost all samples obtained prenatally are screened using quantitative polymerase chain reaction (Q-PCR) to exclude

common trisomies. A proportion of centers also continue to offer full karyotyping and, depending on the type of structural malformation noted, target testing for specific chromosome anomalies is performed.

The cost-effectiveness of these tests depends upon where arrays sit in the cytogenetic testing process. For instance, if Q-PCR continues to be utilized, then the cost of arrays will be relatively expensive compared with the situation where arrays are introduced as the only source of cytogenetic analysis. Also, the resolution of arrays utilized will be important regarding identification of the proportion of CNVs of uncertain significance. This is likely to affect the uptake of genetic counseling, which will adversely affect the economic costs. With the increasing utilization of this technology, the cost of individual arrays is rapidly falling.

Finally there is an urgent requirement for patient satisfaction and qualitative research into the emotional response in parents with the implementation of such prenatal diagnostic techniques.

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