Recommendations for the use of chromosome microarray in pregnancy

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Introduction

Chromosome microarray (CMA) has been established as a useful and cost-effective diagnostic tool in pregnancy in the context of fetal abnormality or stillbirth.[1,2,3]

The increased resolution of CMA over routine karyotyping results in an increased rate of diagnosis of chromosome abnormality, many of which are sub-microscopic. There is, however, a risk of producing findings where the significance is unknown or where the literature, based on postnatal ascertainment, is consistent with a neuro-susceptibility locus, i.e. an abnormality that may predispose to developmental disability or neuropsychiatric illness, but which is highly variable and unpredictable in effect, and seen in unaffected persons. In the context of a pregnancy, these findings may be difficult to interpret. There is also a small risk of finding pathogenic variants that may not be of relevance to the indications for the test, but that are important to the future health of the child and potentially for the family. These uncertainties have led many countries to delay the introduction of CMA in pregnancy until a national agreement or discussion has occurred.[4]

In the UK, until the beginning of 2014, most prenatal CMA had been performed in the context of a research protocol.[5,6] Findings from these studies indicated the utility of CMA and led to debate on its introduction into routine practice.

An *in silico* targeted analysis approach, which targets known genes and regions, well established to be associated with known syndromes, some of which are associated with fetal pathology, has been reported[7]. This approach will minimise the detection of variants of uncertain significance, but will increase the risk of false negative results.

The Joint Committee on Genomics in Medicine (JCGM) is a joint committee of The Royal College of Physicians, The Royal College of Pathologists and the British Society of Genetic Medicine. Its membership includes representation from the Public Health Genomics Foundation, The Royal College of Obstetricians and Gynaecologists, British Maternal and Fetal Medicine Society and the Genetic Alliance.

At the instigation of Dr Diana Wellesley, the JCGM organised a multidisciplinary meeting entitled 'New genomic technologies and pregnancy' on 25 February 2014 at The Royal College of Pathologists. The proceedings of the meeting are available on www.rcpath.org/meetings/college-conferences/internal-conferences-archive/2014. The programme surveyed the current UK experience and considered the issues outlined above. The participants supported the use of CMA in pregnancy in the context of fetal abnormality or increased nuchal translucency (≥3.5 mm), and the development of a national approach to the introduction of this technology into routine practice.

Following the meeting, a number of electronic working groups were established, supported by an oversight group (Appendix 1), with the aim of developing written national guidance by December 2014. This resulting guidance is, of necessity, based on current knowledge, and may change as more experience is accumulated.

Group 1: Care Pathway

The group was asked to consider:

a) the indications for testing (including if a nuchal translucency of≥3.5 mm, which currently affects pathway of care, is an appropriate indication and whether to include ultrasound 'soft markers')

b) an appropriate repository for clinical and laboratory data

c) the benefit from always obtaining parental samples at the outset.

Recommendations

1. Indications

In fetuses where conventional karyotyping by amniocentesis or chorionic villus sampling (CVS) has been indicated in the past, and qfPCR is normal, CMA testing is indicated if:

i. one or more structural anomalies identified on an ultrasound scan

ii. an isolated nuchal translucency NT≥3.5 mm when crown-rump length measures from 45 mm to 84 mm (at approximately 11 weeks 0 days to 13 weeks 6 days)

iii. fetuses with a sex chromosome aneuploidy that is unlikely to explain the ultrasound anomaly (e.g. XXX, XXY and XYY).

This does not include 'soft markers', if at present conventional karyotyping would not be indicated.

These indications for testing will require updating as further evidence becomes available on the diagnostic use of CMA in pregnancy.

2. Clinical and laboratory data repository

The new 'Database of Chromosomal Imbalance and Phenotype in Humans using Ensembl Resources' (DECIPHER) framework[8] makes it very easy to extend DECIPHER to incorporate bespoke forms and data beyond the core dataset. Although different software packages are in use by different centres, if a standardised way of recording data could be agreed between all centres, it could be uploaded in an anonymised form with a unique patient identifier as part of a NHS data-sharing initiative. This would allow linkage of clinical and molecular data for consistent national diagnostic interpretation of results.

3. Parental samples

Interpreting CMA results post-natally is helped by obtaining parental samples to assess the significance of novel duplications and deletions which may be identified by testing. The routine obtaining of parental samples will minimise delays in interpreting some test results but will have resource implications.

Maternal cell contamination can now be reliably excluded by qfPCR, without a maternal sample, in most cases.

It is suggested that individual laboratories and their local clinical genetics and fetal medicine services decide if the sending of parental samples at the time of requesting CMA would be appropriate for their service. This may vary with the indications for the test, and will vary with the collective experience of prenatal CMA and ease of communication between clinical genetics and fetal medicine services.

Group 2: Variant determination and reporting

This group considered the platform to be used for CMA, classification of copy number variants (CNVs), well-characterised variants to be always reported and the definition of incidental findings not to be reported.

They were asked to achieve a balance between detection of variants of known significance and benign variant detection rates, and to consider this in the light of the published literature and UK research experience.

The group also considered the likelihood of detecting variants that would be of significance only in adult life and reporting templates for national reporting for uncertain results.

Recommendations

1. Platform for prenatal arrays

It is expected that most labs will choose to centre their prenatal CMA service around the platform they currently have in place for postnatal arrays.

It is suggested that prenatal array platforms conform to the European consensus.[4,9] Furthermore international consensus has been established for a lower limit threshold of 400 kb across the genome in postnatal application.[10]

2. Recommendations for CMA coverage and probe density

i. In order to achieve sensitivity greater than a karyotype, CMA must have uniform coverage to detect all areas of imbalance at a resolution exceeding that of a karyotype (~5 Mb).Currently, to detect CNV, we recommend using a microarray platform capable of detecting a minimum resolution of ~400 kb throughout the genome as a balance of analytical and clinical sensitivity.

ii. For oligonucleotide and SNP (Single nucleotide polymorphisms) arrays, multiple consecutive probes are needed to permit a call to be made, so the array must be designed to include sufficient probe density for each targeted region. Note that SNP arrays may require a greater number of consecutive probes to permit a reliable call to be made.

iii. Laboratories that implement CMA designs with added targeted coverage in known disease associated genes and regions (e.g. OMIM morbid genes and 'DDG2P' genes)[11] should explicitly state the specific design and mean minimum detection threshold for targeted regions.

iv. In addition, laboratories should be aware of the sensitivity of detection of mosaic findings and ensure that service users are aware that differences may exist in detection of mosaicism between conventional karyotyping and CMA.

3. Classification of CNVs

The consensus is that labs should be moving towards using the 1–5 classification in common use for sequence variants, and recently recommended for CNVs by the American College of Medical Genetics,[12] but also with consideration as to whether the variant is specifically relevant to the referral indication or represents an incidental finding.

4. Variants to be always reported

Any variant that will potentially inform the management of the pregnancy, or of the family, in the clinical context in which CMA was done or in the future, should be reported regardless of size of imbalance.

This includes pathogenic variants related to the indication for CMA but may also include:

- high penetrance neuro-susceptibility loci that are associated with a risk of a severe phenotype to enable discussion about the overall likely phenotype of the child[4]
- neuro-susceptibility loci associated with an increased incidence of anomalies detectable on scan, as reporting these may help direct further scanning[4]
- unsolicited pathogenic findings fulfilling the above criteria. Examples would be:

- deletion of a known cancer predisposition gene, e.g. BRCA1. This recommendation is made on the basis of considering the welfare of the child, to enable parents to benefit from screening or prophylactic treatments if available. This is a rare occurrence, with 27 CNVs affecting cancer genes among 9005 subjects in one study, giving an incidence of 0.30%.[13] There will, however, be differences in detection of medically actionable incidental findings with CMA due to different array platforms, number and genomic position of interrogating probes, CNV size cut-offs, differing classifications of pathogenic findings and variants of unknown significance
- deletion of the dystrophin gene in a female fetus, again to allow the mother to be tested for carrier status and choose testing in any future male pregnancies.

5. Definition of incidental findings not to be reported

Any finding that is not linked to potential phenotypes for the pregnancy (future child) in question or has no clinically actionable consequence for that child or family in the future, e.g. variants of uncertain significance (VOUS) that cannot be linked to a potential phenotype on the basis of genes involved, low penetrance neuro-susceptibility loci and unsolicited pathogenic variants for which there is no available intervention.

The specific variants that would routinely fall into this category include:

- 15q13.1q13.3 duplications
- 15q11 BP1-BP2 duplications or deletions
- Xp22.31 (STS) duplications
- 16p13 duplications
- heterozygous deletion of recessive genes that cannot be linked to the presenting phenotype.

6. Reporting templates for uncertain results

Reporting should broadly follow the recommendations for postnatal array reporting, with two additional recommendations:

i. reports on pathogenic CNVs, particularly neuro-susceptibility loci, should not typically refer to patient support group leaflets, as the available information is best discussed in the context of a clinical genetics consultation

ii. clinically actionable unsolicited pathogenic CNVs should be accompanied by a clear comment that they are unrelated to the presenting problem but that referral to clinical genetics should be considered at an appropriate time.

Appendix 3 is a current list of variants that conform to the categories described in Sections 3 and 4 above and accord with information available at this time.

Group 3: Role and composition of expert advisory group for variants of possible pathogenicity with limited published evidence base

Recommendations

The group would have a role in reviewing:

- unexpected incidental findings
- VOUS not on the reported list

- duplications of known genes with poorly delineated phenotypes
- deletions or duplications of non-OMIM morbid genes
- deletions or duplications of recessive genes tenuously linked to the fetal phenotype
- X-linked or recessive carrier states.

As for the Evaluation of Array Comparative Hybridisation in the prenatal diagnosis of fetal anomalies (EACH) study, the result will need to be referred to the panel once the parental findings are available. The panel should operate in the following way.

- Two clinical scientists and two clinical geneticists per referral, with a maximum turnaround time of 2–3 days for each decision. Where opinions are split, further colleagues may be co-opted to provide additional views.
- A written 'report' will need to be provided by each reviewer to explain their decision. These will be collated and recorded by date, to refer to should there be any queries and to help inform future decisions.
- Where possible, feedback should be provided by the enquiring laboratory as to the pregnancy outcome for inclusion in the Review Panel database.
- Decisions made should be presented for discussion at the annual JCGM update meeting to aid future approaches.

The first main role will be to select and invite clinicians and scientists to join the review panel.

It is acknowledged that as experience of CMA in pregnancy increases and as more data is collated and shared by means of a national database, the need for an expert group is likely to decrease. It is also acknowledged that many services have a well-developed multidisciplinary approach to interpreting and reporting laboratory findings, and that this should be encouraged and developed further to take account of new technologies.

The proposed expert group is an additional optional resource, which may have a particular role in liaising with colleagues working in this area internationally.

Group 4: National information sheet and consent form

Recommendation

To support best practice, a sample consent form and information sheet was developed (see Appendix 2), based on those currently in use in Birmingham and Oxford.

Group 5: Obstetric workforce and genetic counsellor education

Recommendations

The group defined the aims of prenatal microarray education as providing understanding on:

- the technical aspects of a CMA
- the benefits of prenatal CMA
- the limitations and difficulties involved in prenatal CMA
- the indications for requesting CMA
- knowledge of the agreed workflow process

- confidence in explaining a CMA to a patient
- how to give the normal results and conveying these results in context of a pregnancy complicated by structural anomalies
- know how abnormal results/VOUS are given by the clinical genetics team and the relationship between the laboratory and clinical team to establish the significance of the result
- clear contact details with local genetics team.

The group considered that this would need to be a national programme, ideally delivered both face to face and online, with regular provision of updates. They suggested that educational initiatives may need to be extended to other professional and patient groups. Suitable educational resources may already have been developed throughout Europe and should be considered. The group considered that the resources developed will also be useful as other new genomic technologies are developed, as many of the underlying issues of interpretation, unexpected findings and variability will be the same.

Summary

The working groups have made a series of recommendations for the introduction of CMA in pregnancy across the UK, following a multi-disciplinary workshop. These are not intended to duplicate laboratory best-practice guidelines, and have followed a different process. The focus has been on achieving an evidence-based and consistent approach to the indications for testing, professional education, consent and patient information, the laboratory platform and variant interpretation and reporting. Achieving this has differed in the extent of clinical involvement, recognising the complexity of the diagnostic and counselling issues that may result from CMA in the prenatal setting. The recommendations conform in most ways to that of Vanakker *et al* reporting on practice in Belgium.[4]

It is suggested that as a follow up to this process, a Fetal Genetics group is established (Appendix 4). Meanwhile, a trial is planned in three centres of submission of fetal phenotype data to DECIPHER.

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Appendix 1 'New genomic technologies in pregnancy' workshop: Follow-up groups

Follow-up oversight group

Dr Hilary Burton
Professor Alan Cameron
Professor Jill Clayton-Smith
Dr John Crolla
Professor Frances Flinter, Chair of Genetics Clinical Reference Group (CRG)
Dr Bronwyn Kerr
Professor Mark Kilby
Professor Steve Robson, Chair of Fetal Medicine CRG
Dr Anneke Seller
Dr Ros Skinner, Chair of UK Genetic Testing Network

Working group 1: Care pathway

Chair: Dr Carol Gardiner
Dr Janet Brennand
Professor Mark Kilby
Dr Katrina Prescott
Dr Alec McEwan

Working group 2: Variant determination and reporting

Chair: Dr Alison Male
Anita Bruce
Morag Collinson
Dr Melita Irving
Dominic McMullan
Deborah Morrogh
Anna Middleton
Dr Richard Scott
Ingrid Simonic
Sally Taffinder
Dr Jonathan Waters

Working group 3: Role and composition of expert advisory group for variants of possible pathogenicity with no or limited published information

Chair: Dr Diana Wellesley
Dr Elizabeth Sweeney
Dr Oliver Quarrell
Dr Lorraine Gaunt

Working group 4: National information sheet/consent form

Chair: Dr Tara Clancy
Dr Bruce Castle
Professor Mary Porteus
Dr Mousa Hatem

Working group 5: Obstetric workforce and genetic counsellor education

Chair: Dr Deirdre Cilliers
Ms Laura Boyes
Dr Brenda Kelly
Dr Mark Kroese
Dr Denise Williams

Appendix 2 Sample information sheet and consent form

Prenatal chromosome microarray: Information for parents

What is prenatal chromosome microarray?
Prenatal chromosome microarray (CMA) is a test used to pick up chromosome changes which are too small to be seen by the standard tests available in pregnancy.

What are chromosomes?
Chromosomes are structures which carry genes, and genes are instructions to tell the body how to develop and function. Each cell in the body has 46 chromosomes in 23 pairs. We inherit one member of each chromosome pair from each parent. Girls have two X chromosomes (XX) and boys have an X and a Y chromosome (XY). The other chromosome pairs are numbered from 1 to 22. Having too much or too little chromosomal material usually causes significant problems in development.

Why has chromosome microarray (CMA) been offered to you?
Ultrasound scans have shown that your baby has an increased risk of too much or too little chromosomal material. Microarray is a laboratory test that is used to see if the baby has a chromosome change which may explain the ultrasound findings.

What are the advantages of microarray?
The main advantage of microarray is that it can detect very small chromosome changes which cannot be seen by the standard chromosome test. These changes are called micro deletions (tiny pieces of missing chromosome) and micro duplications (tiny pieces of extra chromosome). A change in the chromosomes may explain the ultrasound findings and allow more precise information to be given about what this means for your baby.

What are the disadvantages and limitations of microarray?
Microarray does not detect all chromosome changes as some are too small to be identified at the present time. Some conditions are caused by changes in individual genes. Microarray cannot detect tiny changes in individual genes.

Sometimes results can be difficult to interpret unless a blood sample from both parents is available for comparison.

Microarray may detect changes called ‘variants of unknown significance’. This means there is not yet enough information available to know if these are significant or not. Where there is uncertainty, these variants will not be reported.

Why do some people choose not to have microarray?
Microarray may occasionally identify a chromosome change which is not related to the ultrasound findings but which may have implications for the future health of your baby and possibly for other family members. For example, it may show your baby will have an increased risk of cancer later on in life. Some people do not want to know this sort of information.

What happens next if I have the test?
The first part of the test looks for trisomy 13, 18 and 21. If none of these are seen, the second part of the test, the microarray, will be done. The result will be available in about 2 weeks. The specialist midwife will contact you when it is available.

If any chromosome changes are identified, you will be offered an appointment with a clinical geneticist and genetic counsellor to discuss the result. Both parents may be asked to provide a blood sample to help interpret the test result.

Further questions
If you have more questions about the microarray test, please ask the doctors or midwives in the Fetal Medicine Unit.

Sample consent form

Patient sticker

Patient agreement for prenatal chromosome microarray

Responsible health professional: .....

Special requirements (e.g. other language/other communication method): .....

.....

Name of proposed procedure: **Prenatal chromosome microarray**

STATEMENT OF HEALTH PROFESSIONAL (to be filled in by health professional with appropriate knowledge of proposed procedure as specified in consent policy)

☐ I confirm that I am capable of undertaking this procedure

☐ I confirm that whilst I am unable to undertake this procedure, I have received specific training to obtain consent for this procedure

I have explained the procedure to the patient. In particular, I have explained:

- the intended benefits:

☐ to help explain the ultrasound scan findings

☐ to give more precise information about what this means for the baby

- serious or frequently occurring risks:

☐ not all small chromosome changes can be detected

☐ tiny changes in individual genes cannot be detected

☐ results can be difficult to interpret and sometimes a blood sample from both parents is needed for comparison

☐ changes called ‘variants of unknown significance’ may be found. There is not enough information to know if these are significant. Where there is uncertainty, these variants will not be reported

☐ the test may show a finding which is not related to the ultrasound findings but which may have implications for the future health of the baby (for example an increased risk of cancer later on in life) and possibly for other family members

☐ the patient has been given the **Prenatal Chromosome microarray leaflet**

Signed: .....Date: .....

Name (please print): .....

Job title: .....

Contact details (if patient wishes to discuss options later).....

STATEMENT OF INTERPRETER (where appropriate)

I have interpreted the information above to the patient to the best of my ability and in a way in which I believe he/she can understand.

Signed: .....Date: .....

Name (please print): .....

Copy accepted by patient? Yes / No (please circle)

STATEMENT OF PATIENT

Please read this form very carefully. If your treatment has been planned in advance, you should already have your own copy of page 1 of this form, which describes the benefits and risks of the proposed treatment. If not, you will be offered a copy now.

If you have any further questions, do ask – we are here to help. You have the right to change your mind at any time, including after you have signed this form.

I agree to the procedure or course of treatment described on this form.

I understand that you cannot give me a guarantee that a particular person will perform the procedure. The person will, however, have appropriate experience.

I understand that where tissue material or a specimen is obtained, it may be used for teaching, research of public health monitoring.

Patient's signature: .....Date: .....

Name (please print name): .....

A witness should sign below if the patient is unable to sign but has indicated his or her consent.

Patient's signature: .....Date: .....

Name (please print): .....

Relationship to patient: .....

CONFIRMATION OF CONSENT (to be completed by a health professional when the patient is admitted for the procedure, if the patient has signed the form in advance)

Signed: .....Date: .....

Name (please print): .....

Job title: .....

Important notes (tick if applicable):

Patient has withdrawn consent (ask patient to sign/date here).

Patient's signature: .....Date: .....

Appendix 3 Copy number variants (CNVs)

Susceptibility CNVs to report

CNV	Size	Gene	OMIM	Penetrance* %	De novo* %	Ultrasound findings	Phenotype
Distal 1q21.1 del	1.35 Mb	GJA5	612474	36.9 (23–55)	18–20	CHD, eye, microcephaly	ID, ASD, E
Distal 1q21.1 dup	1.35 Mb	GJA5	612475	29.1 (16.9–46.8)		CHD, eye, macrocephaly	ID, ASD, SCZ
15q13.3 del	1.5–2 Mb	CHRNA7	612001	80.5		(CHD)	ID, ASD, E, SCZ
Distal 16p11.2 del	220 kb	SH2B1	613444	62.4 (26.8–94.4)	30–33.3		ID
Prox 16p11.2 del	550 kb	TBX6	611913	46.8 (31.5–64.2)	65–70.2	(CHD)	ID, ASD, E
17q12 del	1.4Mb	HNF1B	614527	34 (13.7–70)	55.6–62	Renal and urogenital	ID, ASD,(SCZ)

Susceptibility CNVs not to report

CNV	Size	Gene	OMIM	Penetrance* %	De novo* %	Ultrasound findings	Phenotype
15q11.2 BP1-BP2 del	450 kb	NIPA1	615656	10.4 (8.45–12.7)	0		ID, ASD
15q11.2 BP1-BP2 dup	450 kb	NIPA1	608636				ASD
16p13.11 del	1.5 Mb	MYH11		13.1 (7.91–21.3)	21.7		
16p13.11 dup	1.5 Mb	MYH11					
Proximal 1q21.1 dup	0.5 Mb	RBM8A	612475	17.3			ID
16p12.2 deletion	0.5 Mb	CDR2	136570	12.3			
Xp22.31 dup	1.5Mb	STS					ID
Xp22.33 del	Varies	SHOX					

Consider detailed scan looking for associated anomalies or reporting in a clinical context

CNV	Size	Gene	OMIM	Penetrance* %	De novo* %	Ultrasound findings	Phenotype
22q11.2 dup	1.5/3 Mb	TBX1	608363	21.9 (14.7–31.8)	7–25.5	Bladder exstrophy, (CHD), (CP)	ID
Proximal 1q21.1 del	200 kb	RBM8A	274000	17.3 (10.8–27.4)	0	Absent radius	TAR syndrome
17q12 dup	1.4 Mb	HNF1B	614526	21.1 (10.6–39.5)	22.2	Renal (OA & TOF),	ID, E, ASD (SCZ)

Key

ASD = autistic spectrum disorder
CHD = congenital heart disease
CP = cleft palate
E = epilepsy
ID = intellectual disability
OA = oesophageal atresia
SCZ = schizophrenia
TAR = thrombocytopaenia absent radius syndrome
TOF = trachea-oesophageal fistula
( ) = association less clear

*reference 1 Rosenfeld *et al,* 2013.

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Appendix 4 Fetal Genetics Group draft terms of reference

1. To review the existing guidelines and statements from national bodies that address working relationships and clinical liaison between fetal medicine and clinical genetics.

2. To review current models of care between fetal medicine and clinical genetics.

3. In the light of the findings from these reviews, to appropriately work with The Royal College of Obstetricians and Gynaecologists to produce a joint document which aims to:
   a. describe best practice
   b. propose good models of care, with resource implications
   c. propose models of education and training appropriate for trainees in obstetrics and fetal medicine, trainees in clinical genetics and midwives.

4. The group reports to the British Society of Genetic Medicine and the British Maternal and Fetal Medicine Society, both of which are sent copies of minutes of meetings.