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NHS Foundation Trust

Prenatal array in the UK; achieving a consensus?

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Prenatal array 2014

- Birmingham 2008-2012; Kilby et al. Prospective cohort study fetal structural abnormality
- Abnormal QF-PCR 26%. 1 Mb targeted BAC Array versus karyotype; 243 cases, abnormality rate 4.1% over karyotype (4.9% both abnormal) with VOUS 0.4% (ie 1)
- Qualitative study: “Uncertainty is toxic”

Hillman et al, 2012, 2013

EACH study

- EACH study multicentre 7/2012 to 5/2014
- MRC and NIHR funded
- 1000 cases; nuchal translucency > 3.5 in first trimester or structural abnormality
- Initial QF-PCR, negative cases to standardised whole genome oligoarray,(8x 60K ISCA) with enhanced coverage in syndromic regions. Overall 200kb

EACH study; Feb 2014

- 32% abnormal QF-PCR
- 906 cases array ; 5.8% (52) abnormal chromosomes and array, 30 (3.3%, 17 known syndrome) normal chromosomes and abnormal array, all reported, 14 after referral to expert panel
- 1.6% (14) VOUS, referred to expert panel, none reported, only 1 denovo

EACH expert panel

- Only findings relevant to pregnancy
- Clinical scientists and geneticists
- 28 cases, advised reporting 57% of cases less than 1Mb, 25% greater than 1Mb
- Size alone not helpful
- Do not report list; 1q21.1 del and dup, dup 22q11.2, 16p13.11 del and dup, 15q11.2 BP1-BP2

EACH study

- 12 abnormal chromosomes, N array (3 mosaics, 2 markers with heterochromatin, 6 familial and 2 denovo balanced translocations)? Prenatal significance
- Study reporting, including fetal phenotyping, health economic evaluation, qualitative study of staff and participants, in progress

Guys and St Thomas'

- Prenatal microarray soft ware targeting strategy; QF PCR first; structural abnormality or nuchal >3mm
- Agilent Oligonucleotide 60K array; confirmed by FISH
- Targets established microdeletion syndromes (120Kb resolution) and genomic imbalance >3Mb
- Ahn et al PeerJ2:e354 2014; 342 samples, 23 (6.7%) abnormal; anonymised full analysis of 249 cases abnormality of uncertain significance in 44 (17.7%)

Guys and St Thomas'

- Avoid findings of uncertain significance or clinical significance not relevant to pregnancy
- Smaller CNV more likely to be inherited; 3Mb excludes 97% inherited
- Postnatal only 8% 2-3Mb CNV pathogenic
- Excluded 15q11.2, 1q21.1, proximal 16p11.2
- Use of software configuration makes flexible, including for specific clinical information (TAR)
- Cost effective; 60% cost conventional karyotype
- Avoids counselling cost, toxicity of uncertainty

? a UK consensus

- UK genetic services; 23 RGS, 17 in England, clinical and laboratory services, 1-5 x10^6 people
- BSGM; CGS, AGNC, ACGS, Cancer genetic group, cardiac genetic group
- Disease specific guidelines, national or international eg Vasen et al 2013 Lynch
- NICE; BRCA1 and 2 testing

JCGM

- Joint committee of BSGM, RCP, RCPath
- Rotating chair
- Membership also RCPCH, RCOG, RCGP, Faculty of Public Health, Public Health Genomics Foundation, Genetic Alliance, HEE, DH, NHS England
- Strategic advice relating to genomics

JCGM

- “Consent and Confidentiality in Genetic Practice”, “ Genetic testing of Children”, “Genomics in Medicine”
- February 2013, Dr Diana Wellesley; array CGH into clinical practice, avoiding inequity and variability, maximising benefit and minimising harm
- Workshop RCPath February 2014, 70 attendees, scientists, fetal medicine, clinical geneticists

Prenatal array workshop

Presentations and discussion groups;

Does the evidence support the use of array CGH in pregnancy

Define the patient group

Consider if a national approach is needed, equity, medico-legal, approaches for funding

Prenatal array workshop

- Agree; prenatal arrays should replace karyotyping in pregnancy when there is increased nuchal thickening (3.5mm?), or fetal structural abnormality; QF-PCR should be done first; ? for previous chromosome abnormality and non placental IUGR
- A national approach is desirable
- Recognition that issues will apply to NIPT and exome and whole genome sequencing in pregnancy

Workshop follow-up

- Electronic working groups; Aim; published UK guidance
- National information sheet and consent form
- Care pathway
- Obstetric workforce and GC education
- Variant determination and reporting
- Role and composition of expert advisory group for variants of possible pathogenicity with no published information

National information Sheet and Consent form

- Chair, Dr Tara Clancy with Dr Bruce Castle, Professor Mary Porteus & Dr Mousa Hatem
- Patient information leaflet (Oxford and Birmingham)

  Currently not finalised until it is clear what the national consensus is on incidental findings

  Consent Form

  Procedure specific consent form which FMU colleagues happy with

  Signed by both patient and health professionals

  The two issues that may require amendment are the reporting of incidental findings and parents being aware that that genetic information that may be important to other family members can be revealed with their consent.

What is prenatal Array CGH?

Prenatal array CGH (comparative genome hybridisation) is a test used to pick up chromosome imbalances 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 chromosome 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 array CGH been offered to you?

Ultrasound scans have shown that your baby has an increased risk of too much or too little chromosomal material. Array CGH is used see if the baby has a chromosome imbalance which may explain the ultrasound findings.

What are the advantages of array CGH?

The main advantage of array CGH is that it can detect very small chromosome imbalances which can't be seen by the standard chromosome test. These imbalances are called microdeletions (tiny pieces of missing chromosome) and microduplications (tiny pieces of extra chromosome).

An imbalance 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 array CGH?

Array CGH does not detect all chromosome imbalances as some are too small to be identified at the present time.

Some conditions are caused by changes in individual genes. Array CGH 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.

Array CGH 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.

Array CGH may identify a chromosome imbalance 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. Please let us know

if you **only** want to know about imbalances related to the ultrasound findings

or

if you **also** want to know about imbalances with implications for the future health of your baby and possibly other family members

Comment [t1]: Use if national consensus is to give parents a choice

Why do some people choose not to have array CGH?

Array CGH may identify a chromosome imbalance 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.

Comment [t2]: Use if national consensus is to disclose all information that is causal/clinically significant

What happens next?

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 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 imbalances are identified you will be offered an appointment with a Clinical Geneticist and Genetic Counsellor to discuss the result. The baby's father may be asked to provide a blood sample to help interpret the test result.

Consent for Prenatal Array CGH

Part 1 – to be completed by the patient in all cases

Please read this consent form carefully. It describes the intended benefits, limitations and risks of prenatal array CGH. You have the right to change your mind, including after you have signed this form, by contacting the person who has explained the test to you. You should be given your own copy of this consent form to take away.

I have had the following explained to me

Name of purposed test: prenatal array CGH

Please initial the boxes

The intended benefits of the test:
□ to help explain the ultrasound scan findings
□ to give more precise information about what this means for the baby

The limitations of the test:
□ not all chromosome imbalances can be detected
□ tiny changes in individual genes cannot be detected
□ results can be difficult to interpret unless a blood sample from both parents is available 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 possible risks of the test
□ the test may show a chromosome imbalance which is not related to the ultrasound findings but which may have implications for the future health of the baby and possibly for other family members

Consent for testing and any restrictions imposed:
□ I agree to the proposed test as above and
Either
□ I **only** want to know about imbalances related to the ultrasound findings
Or
□ I **also** want to know about imbalances with implications for the future health of your baby and possibly other family members

I understand that the result may enable family members to benefit from genetic testing.
Either
□I give consent for genetic information that may be important to other family members to be made available to their doctor.
Or
□ I do not give consent for genetic information that may be important to other family members to be made available to their doctor.

□ I understand that a blood sample from the father may be necessary to help interpret the result

I have been counselled in relation to:
□ not having prenatal array CGH
□ chorionic villus sampling
□ amniocentesis
□ fetal blood sampling

I understand that
□ there is a small risk of the procedure causing miscarriage.
□ there is a small risk of the test failing to give a result

Please sign below

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

Name (PRINT): .....

Consent for Prenatal Array CGH

Part 2 MUST be completed by the Health Care Professional obtaining consent

Nature of test required:
□ CVS
□ amniocentesis
□ fetal blood

Statement of health professional (to be completed by a health care professional with appropriate knowledge of proposed procedure):

I have explained the procedure to the patient. In particular, I have discussed, as outlined on page 1:

□ the intended benefits

□ the limitations

□ the possible risks

Informed consent has been given, with any restrictions indicated on page 2 of this form.

□ I have also discussed what prenatal array CGH and the PND procedure is likely to involve, the benefits and risks of any available alternative tests (including no test) and any particular concerns of those involved.

□ I have provided the patient with a signed copy of this consent form

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

Name (PRINT). .....

Job title: .....

CONTACT TELEPHONE NUMBER: .....

Care Pathway Group

- Chair Dr Carol Gardiner, Professor Mark Kilby, Dr Katrina Prescott, Dr Janet Brennand, Dr Alec McEwan, Dr Alan Mathers, Dr Fiona Mackenzie, Dr Dominic McMullan & Dr Angela Douglas
- To consider indications for testing
- To include development of a repository for clinical and laboratory data
- To consider whether it should be mandatory to obtain samples from both parents before testing

Care Pathway Group

1. To consider indications for testing

Fetuses (singleton or dichorionic twin) undergoing conventional karyotyping by amniocentesis or Chorionic Villus Sampling (CVS) with a normal qfPCR result for clinical indications including:

one or more structural anomalies identified on an ultrasound scan

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)

The parents of fetuses with a sex chromosome aneuploidy that is unlikely to explain the ultrasound anomaly e.g. XXX, XXY and XYY will also be offered prenatal array CGH.

These indications for testing will require updating as further evidence becomes available on the diagnostic use of a-CGH.

Care Pathway Group

- **To include development of repository for clinical and laboratory data**

  The new DECIPHER framework 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 the NHS data sharing initiative.

  There are other software archiving systems to classify fetal anomalies (i.e. Cartigenia) and the national decision is around the benefits of a national database linking clinical and molecular data.

- **To consider if parental samples should always be obtained before testing can commence**

  Interpreting a-CGH results postnatally is helped by obtaining parental samples to asses the significance of novel duplications and deletions which are identified by testing.

  A sample from the mother should be mandatory to be obtained at the time of the invasive test but if possible, samples from both parents should be sent with the invasive prenatal sample when a-CGH is requested

Obstetric Workforce and GC Education

- Chair Dr Deirdre Cilliers, Ms Laura Boyes, Dr Brenda Kelly & Dr Denise Williams
- Main aims of Prenatal microarray education would be ro understand :

  The technical aspects of a microarray

  The benefits of prenatal microarray

  The limitations and difficulties involved in prenatal microarray

  The indications for requesting microarray

  Knowledge of the agreed workflow process

  Confidence in explaining a microarray to a patient

  Confidence in taking consent from 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

  Have clear contact details with local genetics team

Obstetric Workforce and GC Education

- There needs to be a nationally led programme for Obstetricians, Midwives, Clinical Geneticist and Clinical Genetic trainees and Genetic Counsellors
- Teaching should be both seminar/workshop for and on-line with regular updates for both Obstetricians, obstetric and Clinical Genetics trainees, midwives and genetic counsellors

Obstetric Workforce and GC Education

- Although this is not part of the remit, public education could be considered by the committee. Various established charities may be involved, e.g. Unique or ARC.
- Other health professionals may require education e.g. GPs.
- We can learn from others- European colleagues and others may prove a helpful resource as some already have an established clinical prenatal microarray service.
- This education programme may be helpful for the introduction of further genomic technology into prenatal practice, when these are due for implementation into clinical service.

Variant Determination and Reporting Working Group

- Dr Alison Male (Chair), Melita Irving, Dominic McMullan, Deborah Morrogh, Ingrid Simonic , Anita Bruce, Anna Middleton, Richard Scott, Sally Taffinder & Jonathan Waters
- The guidelines were for the reporting of prenatal arrays in the context of abnormal prenatal scan findings *not* as a screening tool.
- The group sought to find a balance between answering the clinical question about the likely phenotype of the child whilst minimising any additional anxiety that might arise from the reporting of unsolicited findings.
- The term “unsolicited findings” includes
  - variants of uncertain significance (VOUS),
  - pathological variants with variable expression or penetrance (neurosusceptibility loci)
  - known pathological variants that are unrelated to the presenting anomalies (incidental findings).

Variant Determination and Reporting Working Group

- **1. Platform for prenatal arrays**

  It is expected that most labs will choose to centre their prenatal array service around the platform in place for post-natal.

  It is suggested that prenatal array platforms conform to the European consensus - arrays should aim to detect any imbalance greater than 500kb.

- **2. Classification of CNVs**

  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 ACMG but also with some indication as to whether the variant is relevant to the referral indication.

Variant Determination and Reporting Working Group

- **3. Variants to be always reported**

  Any variant that will potentially inform the management of the pregnancy or of the family, in the context in which the array was done or in the future.

  This includes pathological variants related to the indication for array but may also include:

- High penetrance neurosusceptibility loci that are associated with a risk of a severe phenotype to enable discussion about the overall likely phenotype of the child (Vanakker et al, 2014).
- Neurosusceptibility loci associated with an increased incidence of anomalies detectable on scan as reporting these may help direct further scanning.

  (Vanakker et al 2014)
- Unsolicited pathological findings fulfilling the above criteria.

  Examples would be

  Deletion of known cancer predisposition genes eg *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.

  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.

Variant Determination and Reporting Working Group

- **4. Definition of incidental findings not to be reported**

  Any finding which 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.

  eg VOUS that cannot be linked to a potential phenotype on the basis of genes involved, low penetrance neurosusceptibility loci, and unsolicited pathological variants for which there is no available intervention. The 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

Variant Determination and Reporting Working Group

- 5. **Reporting Templates for uncertain results**

  Reporting should broadly follow the recommendations for postnatal array reporting.

  There are only two additional recommendations made here.
- The first is that reports on pathological CNVs, particularly neurosusceptibility loci should not typically refer to patient support group leaflets and the available information is felt best discussed in the context of a Clinical Genetics consultation.
- Secondly, clinically actionable unsolicited pathological findings 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.

Role and composition of expert advisory group for variants of possible pathogenicity with no published information

- Dr Diana Wellesley (Chair), Dr Elizabeth Sweeney, Dr Oliver Quarrell & Dr Lorraine Gaunt
- The group would have a role in reviewing :
- Unexpected incidental findings, VOUS not on the reported list, duplications of known genes with poor phenotypic experience, deletions or duplications of non-OMIM morbid genes, perhaps dels or dups of recessive genes tenuously linked to the fetal phenotype and some XL or recessive carrier states
- As for the EACH study, the result will need to be referred to the panel once the parental findings are available.
- 2 scientists and 2 clinicians per referral, turnaround time 2-3 days max for each decision and where opinions are split, further colleagues may be co-opted in to provide additional views.
- A written 'report' will need to be provided by each reviewer to explain their decision which will be collated and recorded, by date, 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.
- The 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

Outcomes

- Discussion at BSGM 23/9/2014
- Support for overall concepts
- Support for an unmasked approach
- Recognition that resource for full disclosure or choice (ie pre test counselling by clinical genetics) does not exist
- Give results related to the phenotype and clinically actionable incidental findings
- Development of guideline list for VOUS and IF may be helpful
- Local expert groups in operation, formal national may not be required

Outcomes

- UK guideline to be published by 12/2014
- Development of a UK Prenatal Genetics (?Genomics) group; best practice fetal medicine and clinical genetics, models of care, training across specialties and different professional groups, introduction of new genomic technologies, education.

Particular issues

- Closer working between clinical geneticists and clinical scientists
- Sharing of fetal phenotype/genotype data
- Extending knowledge of phenotypes to conception
- Education of midwives and obstetricians
- A level of comfort with uncertainty and Do Not Report decisions and recommendations

Thank you to:

- **JCMG Oversight Group**

  Dr Bronwyn Kerr, Dr Hilary Burton, Dr John Crolla, Dr Anneke Seller, Professor Mark Kilby, Professor Alan Cameron, Professor Jill Clayton-Smith with additions of Professor Francis Flintner, Chair Genetics CRG and Professor Steve Robson, Chair Fetal Medicine , Dr Ros Skinner, Chair UKGTN

- **National Information Sheet and Consent form Group**

  Chair, Dr Tara Clancy with Dr Bruce Castle, Professor Mary Porteus & Dr Mousa Hatem

- **Care Pathway Group**

  Professor Mark Kilby, Dr Katrina Prescott, Dr Janet Brennand, Dr Alec McEwan, Dr Alan Mathers, Dr Fiona Mackenzie, Dr Dominic McMullan & Dr Angela Douglas, Dr Carol Gardiner

- **Obstetric Workforce and GC Education Group**

  Chair Dr Deirdre Cilliers, Ms Laura Boyes, Dr Brenda Kelly & Dr Denise Williams

- **Variant Determination and Reporting Working Group**

  Dr Alison Male (Chair), Melita Irving, Dominic McMullan, Deborah Morrogh, Ingrid Simonic , Anita Bruce, Anna Middleton, Richard Scott, Sally Taffinder & Jonathan Waters

- **Role and composition of expert advisory group for variants of possible pathogenicity with no published information Group**

  Dr Diana Wellesley (Chair), Dr Elizabeth Sweeney, Dr Oliver Quarrell & Dr Lorraine Gaunt

- **All Clinical Genetics Services in UK**