Copy Number Variants of Uncertain Significance in Prenatal diagnosis
Are the Goalposts Moving?

Lisa Burvill-Holmes
Bristol Genetics Laboratory
Microarray CGH in Prenatal Diagnosis

- 2012 to 2014
  Evaluation of Array Comparative Genomic Hybridisation in Prenatal Diagnosis of Fetal Anomalies

- Strict criteria to aid in the reporting decision making process with an expert review panel to offer advice

- Variants of unknown significance detected in 1-2%

New Genomic Technologies and Pregnancy
Tuesday 25 February 2014

- General consensus that findings of uncertain significance should not be reported in a prenatal setting

Recommendations for the use of chromosome microarray in pregnancy
Bristol Prenatal Diagnosis

- Initial pilot project – microarray CGH offered to hospitals
- At the same time limiting testing for pregnancies referred for Downs risk only, molecular testing and other opportunist samples to an aneuploidy test by QFPCR only
- Rolled out the use of microarrays for abnormal scan referrals to all centres in the South West.

Copy number variant identified

- No strong evidence for pathogenicity
  - No not report
- Clear evidence for pathogenicity
  - Report
- Weak evidence for pathogenicity or evidence of variable penetrance or expressivity
  - Contact clinical genetics for advice prior to writing the report
Scan findings VSD, PA>AO

- 111kb deletion of 10q23.1 - GRID1

- Within the much larger 10q22q23 microdeletion syndrome
  - phenotype that includes developmental delay, macrocephaly, cerebellar anomalies, dysmorphism and cardiac defects.
  - Van Bon et al (2011) proposed that GRID1 and BMPR1A may be candidate genes for the cardiac involvement in this syndrome.
  - GRID1 has also been implicated being causative for Schizophrenia in several association studies.

- Our deletion was **intrinsic and paternally inherited**
  - therefore may be unrelated to the scan findings - clinical genetics recommended reporting to the referring obstetrician
Scan finding - hypoplastic left heart

- A 69kb deletion of 2p16.3 within an intron of NRXN1
  - NRXN1 deletions -neurosusceptibility loci with incomplete penetrance
  - no compelling evidence that intronic deletions are causative of a phenotype and so this was not reported

- A 19kb duplication of Xp22.2 - MID1
  - non-coding region (5’upstream sequence)
  - mutations cause X linked Opitz GGGB syndrome
    • characterized by hypertelorism, hypospadias, cleft lip/palate, laryngotracheoesophageal abnormalities, imperforate anus, developmental delay, and cardiac defects

- The foetus was female and the duplication was maternally inherited
  - Consideration of the high ‘burden’ of a child with Opitz GGGB syndrome and heart defects are associated with this syndrome clinical genetics recommended reporting
  • This finding was not clearly pathogenic, it may have been related to the abnormalities in the foetus
  • Differences in activation status of the X chromosome between the foetus and the mother could give rise to a different clinical presentation
Scan finding - short femurs

- 300kb duplication of 10q23.2 which included the genes \textit{BMPR1A} and \textit{GLUD1}

- \textit{BMPR1A} - Point mutations, deletions and some duplications of this gene have been reported in association with Juvenile Polyposis syndrome (OMIM#174900) which presents with multiple gastrointestinal polyps and an increased risk of colon cancer

- \textit{GLUD1} - Mutations of have been reported in association with Hyperinsulinism/Hyperammonia syndrome (OMIM#606762) which is an AD disorder whereby episodes of hypoglycemia lead to seizures and mental retardation.

- Neither of these findings were thought to be related to the scan findings and the duplication was shown to be \textit{maternally inherited}, but clinical genetics agreed that the duplication was reported
Flexed lower limbs and soft markers

- Previous CVS raised Downs risk (NT 2.7mm)
- 484kb deletion of the TAR region at 1q21.1
- This deletion when identified *in trans* with a hypomorphic variant in the *RBM8A* gene gives rise to TAR syndrome
  - Bilateral radial aplasia and platelet deficiency causing thrombocytopenia
  - lower limb abnormalities are also sometimes seen.
- no hypomorphic variant of *RBM8A*
  - unlikely that this foetus was affected by TAR syndrome
- There is **limited evidence that deletion** of this region in individuals without hemizygosity for the hypomorphic variant of *RBM8A* or features of TAR syndrome may contribute to a **variable, abnormal phenotype which may include neurodevelopmental defects**
- This finding was reported
Have concerns about reporting changed?

• The landscape of prenatal diagnosis has changed certainly locally and probably nationally since that multidisciplinary meeting in February 2014.

• Prenatal diagnosis has changed from a genome wide analysis by chromosome analysis on a wide range of pregnancies where the indication for testing has been a high Downs risk - the majority no abnormal findings on scan

• These pregnancies are now only offered a rapid aneuploidy test  
  – Followed by karyotype if QFPCR is abnormal

• Pregnancies with a family history of chromosome abnormality or parental balanced rearrangement
• Maybe the history explains the initial concern about reporting findings on microarray of uncertain significance
• Pregnancies under ongoing microarray analysis are already in a situation of unknown significance
  – there is uncertainty regarding the prognosis
  – especially in the first trimester when scan findings may be limited.

Abnormal ultrasound scan

- may resolve during the pregnancy
- decision to terminate the pregnancy regardless of the results of genetic testing

Good Prognosis

uncertainty

Additional information useful

Termination

Exceptional healthcare, personally delivered
• Perhaps it can be argued that giving additional information even if it does not lead to a definite prognosis may be helpful in allowing couples to make very difficult decisions regarding their pregnancies.

• Whilst working in a multidisciplinary way our experience raises the issues of who to talk to and when

• If there is not national consistency then may we should revisit a national expert review panel

• The principles developed for array CGH should support the use of other genomic technologies in pregnancy as they are developed e.g. Exomes
Acknowledgements

**Laboratory staff at BGL**
Julie-Ann Moore  
Adele Reynolds  
Emily Jones  
Emma Smith  
Eileen Roberts  
Catherine Delmege  
Technical staff

**Clinical Genetics Consultants**
Exeter and Bristol

**Obstetricians**
Antenatal and Foetal Medicine Units in South West