Predicting the Challenges of Prenatal Microarray from the Postnatal Experience

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Microarray Service at SickKids
Annual Microarray Test Volumes

- **Agilent 44K**
- **OGT 180K**

Data categories:
- **Sickkids**
- **Out of Province**
- **MOH**

Time periods:
- 05/06
- 06/07
- 07/08
- 08/09
- 09/10
- 10/11
- 11/12
- 12/13
Interpretation of CNVs

- Pathogenic
- Likely Pathogenic
- Uncertain Clinical Significance
- VUS
  - Del <200 kb
  - Dup <500 kb
- Benign

To be reported

Not Reported
Diagnostic Yield

- Pathogenic = 10%
- Variants of Uncertain Significance = 16%

- Pathogenic = 9%
- Variants of Uncertain Significance = 14%
Challenging Cases
Challenging Case

- Neuropsychiatric Risk Loci
- Insufficient published data
- Large CNVs of Unknown Clinical Significance
- X-linked Loci

- Small CNVs
- ? Involve Exonic Sequences
- Mosaic CNVs
- ? Structural Chromosomal abnormities
**Neuropsychiatric Risk Loci**

<table>
<thead>
<tr>
<th>CNV</th>
<th>Initial Identification</th>
<th>Subsequent neurodevelopmental associations</th>
<th>Other non-behavioural phenotypes</th>
</tr>
</thead>
<tbody>
<tr>
<td>del3q29</td>
<td>MR (Rossi et al., 2001)</td>
<td>ASD (Willatt et al., 2005); schizophrenia (Mulle et al., 2010) BPD (Bailer et al., 2002)</td>
<td>Eye abnormalities (Tyshchenko et al., 2009); cardiac defect (Li et al., 2009)</td>
</tr>
<tr>
<td>del7q31</td>
<td>ASD and language disorders (IMGSAC, 2001)</td>
<td>Speech and language development (Marshall et al., 2008); TS (Sundaram et al., 2010)</td>
<td>Triphalangeal thumb and polysyndactyly phenotype (Kloppoki et al., 2008)</td>
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<tr>
<td>dup7q36.3</td>
<td>ID (Tyson et al., 2005)</td>
<td>Schizophrenia (Kirov et al., 2009a, b)</td>
<td></td>
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<tr>
<td>dup15q11–q13</td>
<td>Autism (Gillberg et al., 1991)</td>
<td>IGE (Bundey et al., 1994); developmental delay (Mohandas et al., 1999); schizophrenia (Kirov et al., 2008; Ingsom et al., 2011)</td>
<td></td>
</tr>
<tr>
<td>del15q11.2</td>
<td>ID, ADHD (Murthy et al., 2007)</td>
<td>Schizophrenia (Stefansson et al., 2008; ISC, 2008); ASD (Doornbos et al., 2009); IGE (de Kovel et al., 2010)</td>
<td></td>
</tr>
<tr>
<td>del15q13.3</td>
<td>ID, seizures (Sharp et al., 2008)</td>
<td>Schizophrenia (Stefansson et al., 2008; ISC, 2008); ASD (Muller et al., 2009); IGE (Helbig et al., 2009); BPD (Miller et al., 2009)</td>
<td></td>
</tr>
<tr>
<td>dup16p11.2</td>
<td>Autism (Weiss et al., 2008)</td>
<td>Schizophrenia (Walsh et al., 2008; McCarthy et al., 2009); ADHD, microcephaly (Shinawi et al., 2010)</td>
<td>Syringomyelia (Schaaf et al., 2011)</td>
</tr>
<tr>
<td>del16p11.2</td>
<td>Cardiac defects and unilateral multiple renal cysts (Hernando et al., 2002)</td>
<td>Mild MR (Chebranian et al., 2007); Autism (Weiss et al., 2008; Kumar et al., 2008)</td>
<td>Flat facies, hypotonia, short stature (Ballif et al., 2007a, b); obesity (Walters et al., 2010)</td>
</tr>
<tr>
<td>del16p13.1</td>
<td>ID (Ullmann et al., 2007)</td>
<td>IGE, microcephaly (Hannes et al., 2009); schizophrenia (Ingason et al., 2009); IGE (de Kovel et al., 2010)</td>
<td>Congenital anomalies (Hannes et al., 2009)</td>
</tr>
<tr>
<td>dup16p13.1</td>
<td>ASD (Ullmann et al., 2007)</td>
<td>MR (Hannes et al., 2009); schizophrenia (Ingason et al., 2009)</td>
<td></td>
</tr>
</tbody>
</table>

Variable phenotype, penetrance and expressivity.
Insufficient Published Data

• 77 Kb deletion, Xq13.3, exonic deletion of KIAA2022. In one published report disruption of KIAA2022 gene has been reported in two related males with intellectual disability.

• 191 Kb deletion, 15q26.1, four RefSeq genes including CHD2. Disruption of CHD2 gene by a de novo translocation in one patient (Kulkarni et al, 2008).

Clinical significance not established.
Insufficient Published Data

KIAA2022
- Cantagrel et al, 2004
- Van Maldergem et al, 2013
- Pathogenic

CHD2
- Kulkarni et al, 2008
- Carvill et al, 2013
- Suls et al, 2013
- Courage et al, 2014
- Chénier et al, 2014
- Pathogenic
Large CNVs of Unknown Clinical Significance

- 1.8 Mb deletion, 11q13.4. Involves 32 RefSeq genes, 05 OMIM Morbid Map genes.

Size and number of genes suggest to be Pathogenic
No published evidence
X-linked Loci

- DMD deletions in females
- 6.708 Mb deletion, Xq27.3-q28, 39 RefSeq genes, 03 OMIM Morbid Map genes FMR1, FMR2 and IDS.

Unpredictable phenotype in females due to X Chromosome inactivation pattern and location of CNV
Very Small CNVs

- 9 Kb deletion, 17p13.3, Exons10-11, PAFAH1B1 (LIS1).

Confirmation by other methods is required.
81Kb intragenic deletion, OMIM Morbid Map gene AUTS2. Exon 4 is deleted?

Confirmation by other molecular methods is required
Mosaic CNVs

- Trisomy 13, 15, 18, X, Y

- Mosaic Deletions and Duplications of Large Segments
  - 15 Mb del at 20q11.21-q13.12, 10 Mb dup at 6q11.1-q13

G-banding and FISH testing to determine the level of mosaicism
Structural Chromosomal Abnormalities

- 32 Mb terminal deletion, Xp22.33-p21.1

G-banding, 45,X, dic(X;21)(p21.1;p11.2)
Reporting Challenging Cases

Interpretation
- Clinical correlation
- Parental testing
- Internal database

Technical
- qPCR
- FISH
- G-banding
Considerations for Prenatal Microarray

**Genetic Counseling**
- Interpretation
  - Neuropsychiatric Risk Loci
  - Insufficient published data
  - Large CNVs of Unknown Clinical Significance
  - X-linked Loci

**Technical**
- Parental Samples
- Streamlined Follow up Tests
  - ? False Positive/Small CNVs
  - ? Involve Exonic Sequences
  - Mosaic CNVs
  - ? Structural Chromosomal abnormalities

Cultured Cells for Follow up Testing
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