Clinical utility of the X-chromosome array

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INTRODUCTION

• ACMG recommends WGA as the first line test:
  * unexplained DD/ID
  * MCA
  * ASDs

• ID, ASDs, LD and DD are more frequent in males.

• High incidence of mutations within X-linked neurodevelopmental genes.
METHODS

• Single site, retrospective review, 2008-2011.
• X array: OGT CytoSure™ 28k, 44k or 105k
• Results: normal, abnormal or inconclusive.
• For CNVs \(\rightarrow\) DGV, confirmation, family studies
• Subdivided patients according to the indication
TOTAL ARRAYS : 94

ASDs/ID/DD with FH: 21 (29.2%)
ASDs/ID/DD without FH: 14 (19.4%)
Define Breakpoints: 7 (9.7%)
Family Studies: 9 (12.5%)
Suspected X-linked: 21 (29.2%)

Clinical: 72

Research: 22

METHODS
RESULTS

• 78% Males

• 35 patients with at least 1 CNV: $\frac{35}{72} = 48.6\%$

• 43 CNVs:
  25 Deletions (58.1%): 0.27Kb-26.5Mb
  18 Duplications (41.9%): 0.91Kb to 300Kb
RESULTS

<table>
<thead>
<tr>
<th></th>
<th>Autism/DD/ID with FH</th>
<th>Autism/DD/ID without FH</th>
<th>Define breakpoints</th>
<th>Family Study</th>
<th>Suspected X-linked condition</th>
<th>TOTALS (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inconclusive</td>
<td>4.7%</td>
<td>0.0%</td>
<td>0.0%</td>
<td>0.0%</td>
<td>0.0%</td>
<td>1.4%</td>
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<tr>
<td>Abnormal Unknown</td>
<td>9.5%</td>
<td>14.3%</td>
<td>0.0%</td>
<td>0.0%</td>
<td>0.0%</td>
<td>5.6%</td>
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<tr>
<td>Abnormal Not significant</td>
<td>19.1%</td>
<td>7.1%</td>
<td>14.8%</td>
<td>11.1%</td>
<td>4.8%</td>
<td>11.1%</td>
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<tr>
<td>Abnormal Significant</td>
<td>0.0%</td>
<td>0.0%</td>
<td>71.4%</td>
<td>55.6%</td>
<td>61.9%</td>
<td>31.9%</td>
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<tr>
<td>Normal</td>
<td>66.7%</td>
<td>78.6%</td>
<td>14.3%</td>
<td>33.3%</td>
<td>33.3%</td>
<td>50.0%</td>
</tr>
</tbody>
</table>
RESULTS

ASDs/DD/ID with Family History (21 cases):

- 5 y/o with DD
- Dysmorphic
- 14Kb duplication at Xq28 includes SLC6A8
RESULTS

ASDs/DD/ID without Family History (14 cases):

• 8 y/o with DD + Behavior
• Dysmorphic
• 2kb duplication at Xq24 includes \textit{CUL4B}
  (Cabezas syndrome)
RESULTS

Suspected X-linked conditions (21 cases)

- **All** clinically suspected:
  - Blue cone monochromatism (BCM)
  - Incontinentia pigmenti (IP)
  - Osteopathia striata with Cranial Sclerosis (OSCS)
  - Wiskott-Aldrich syndrome (WAS)
  - X-linked ichthyosis (XLI)
  - Leri-Weill dyschondrostosis
  - Adrenal hypoplasia congenita with glycerol kinase deficiency (CAH-GKD)
RESULTS: X-Linked conditions

This 0.4Kb deletion would have been missed by SNP 6.0
RESULTS: X-Linked conditions

These 0.6Kb deletions would have been missed by SNP 6.0
RESULTS: X-Linked conditions
RESULTS: X-Linked conditions

Patient (red), Mother (blue), Control (yellow)

This 7Kb deletion was missed by SNP 6.0
WGA vs X-chromosome array

• 27 patients underwent WGA (Affy® SNP 6.0 array and/or OGT® 105K oligo)
• Concordance = 70% (19/27).
  = 1 pathogenic deletion (WTX) missed by WGA
CONCLUSIONS

• The XCA frequently identifies genomic alterations of the X-chromosome.
• Careful interpretation and correlation with clinical findings is needed.
• When used to confirm a suspected X-linked condition, the XCA has a high yield and is useful.
• WGA may not be optimal for detecting very small deletions or duplications of regions/genes associated with an X-linked condition.
Thank you

• Patients and families
• Cytogenetics and molecular labs