ARRAY-CGH IDENTIFIES SUBMICROSCOPIC DUPLICATION OF COMMON MICROLETION REGIONS 7q11.23, 16p13.3, AND 22q11.2
Munroe-Meyer Institute, University of Nebraska Medical Center, Omaha, NE.

CLINICAL FINDINGS IN FIVE CASES OF MICROWULTIPICATION

Introduction

- Chromosome duplication of clinically relevant microdeletion regions is less recognized, in part due to the limited resolution of GW-banding and metaphase FISH analysis and because the phenotypes associated with duplication are not well defined.
- Array-CGH (aCGH) has emerged as a viable technology in the cytogenetics laboratory for the detection of chromosomes deletions and duplications.
- Our laboratory studied 300 patients with developmental delay and/or multiple congenital anomalies (MCA) by aCGH utilizing the Spectral Genomics Constitutional Chip™.

Results

- Twenty one out of 300 studies were abnormal by aCGH analysis.
- Five out of 24 abnormal cases (24%) revealed duplication of known, clinically associated microdeletion regions including 7q11.23 (WS), 16p13.3 (RTS) and 22q11.2 (DG/VCFS).
- Each of these duplications involved the same region that is typically deleted in the reciprocal microdeletion syndrome relative to the specific clones on the array.
- All five cases of duplication were confirmed by interphase FISH analysis.

<table>
<thead>
<tr>
<th>Case #</th>
<th>Age/ Sex</th>
<th>Nomenclature</th>
<th>Patient Clinical Findings</th>
<th>Typical Phenotype Associated with Microduplication</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5 y/o</td>
<td>46,XY; + del 7q11.23 (RP5-1177A1 =&gt; RP11-2260720p3)</td>
<td>Developmental delay, Speech and language delay, Central hypotonia</td>
<td>Developmental delay, expressive speech, Poor visuospatial skills</td>
</tr>
<tr>
<td>2</td>
<td>2 y/o Female</td>
<td>46,XX; + del 16p13.3 (RP11-488A5 =&gt; RP11-60411)x3</td>
<td>Dysmorphic facial features, Prominent epicanthal folds, Heart disease, Hypotonia, Developmental and speech delay</td>
<td>Short stature, Developmental delay, Characteristic facial features, Broad thumbs and toes</td>
</tr>
<tr>
<td>3</td>
<td>6 y/o Female</td>
<td>46,XX; + del 22q11.21 (RP3-493F17 =&gt; RP11-31610)x3</td>
<td>Developmental delay, Muscular hypotonia, vesicourethral reflux</td>
<td>Congenital heart disease, Patent dextrocardia, Immune deficiency, Learning difficulty, Characteristic facial features</td>
</tr>
<tr>
<td>4</td>
<td>6.5 y/o Male</td>
<td>46,XY; + del 22q11.21 (RP3-493F17 =&gt; RP11-31610)x3</td>
<td>Autosomal behaviors, up-slanting of palpebral fissures, macrostomia, strabismus</td>
<td>Same as above</td>
</tr>
<tr>
<td>5</td>
<td>4 y/o Male</td>
<td>46,XY; + del 22q11.21 (RP3-493F17 =&gt; RP11-31610)x3</td>
<td>Behavior problems, minor dysmorphic features, 10 Y delay, speech and language delays</td>
<td>Same as above</td>
</tr>
</tbody>
</table>

Summary

- Case 1 was referred for genetic studies with primary indication of speech delay, a finding contrary to the characteristic "social demeanour" and expressive speech observed WS patients.
- Case 2 shared features of Rubenstein-Taybi syndrome (RTS) yet did not have the hallmark broad thumb that is associated with RTS.
- Three cases with normal karyotype exhibited duplication of 22q11.2 in the DG/VCFS critical region. All three cases shared some of the DG/VCFS characteristics and also had other distinct features.
- Microduplication of commonly microdeletions regions appears more prevalent than previously appreciated hence, independent FISH studies for microdeletion syndromes should include interphase analysis to determine microduplications.

Conclusions

- These cases illustrate the utility of array-CGH investigations especially in chromosomal duplication cases, which, if not identified, may remain as a diagnostic challenge.
- More cases with duplication of commonly microdeleleted regions will be defined as aCGH studies gain momentum in clinical settings.
- As these regions become more defined, a better understanding of the genotype-phenotype correlations of microduplications will emerge.