Letter to the Editor

Utility of chromosomal microarray in five cases with cytogenetic abnormalities detected by traditional karyotype

To the Editor:

Cytogenetic/cytogenomic/chromosomal microarray (CMA) using oligonucleotides to detect copy number variants (CNVs) has been recommended as first tier test in the evaluation of patients with developmental delay/intellectual disability, multiple congenital abnormalities and autistic spectrum disorders (1). Moreover, CMA can provide further information in cases with chromosomal imbalances of unknown origin. In this study, we have described five cases with cytogenetic abnormalities, in which CMA has provided useful additional information.

CMA was performed by the Cytogenetics 2.7M Array, Affymertix® (four cases) and HumanCytoSNP-chip, Illumina (one case). GRch 37: Feb 2009 (hg 19) human genome version was used to annotate the data.

Clinical details of all five cases are presented in Table 1. Various cytogenetic abnormalities included extra unidentified material on one chromosome (cases 1 and 5), cytogenetically balanced translocation (case 2), presence of a marker chromosome (cases 1, 3, and 4) and mosaicism (case 1). In two families (cases 3 and 4) CMA was performed on prenatal samples also, as conventional karyotype results were either not conclusive or to look for submicroscopic rearrangement at chromosomal breakpoints. In case 1, karyotype had shown extra material on 12p, CMA showed gain of 34 Mb in this region suggestive of tandem duplication of this segment. CMA also identified the presence of small (415 kb) loss in the same region pointing toward cryptic chromosomal rearrangement. In the same case, karyotype also showed the presence of a marker chromosome in 15/25 cells. CMA failed to detect the origin of this marker chromosome in mosaic state. Few previous studies also have pointed out that CMA may fail to detect the origin of marker chromosome in as many as >50% of cases, especially if it contains repetitive heterochromatin region which is usually not covered by probes in array platform (2). Case 2 was having cytogenetically balanced de novo translocation between chromosomes 1 and 4. However, CMA showed cryptic deletions at the break points.

In case 3, karyotype of the proband showed the presence of a marker chromosome, CMA report of the proband showed double segmental imbalance involving chromosomes 11 and 22 as shown in Table 1. Karyotype of the mother showed balanced translocation between chromosomes 11 and 22. Amniocentesis and fetal karyotype was done in next pregnancy of the mother. Karyotype result was similar to mother showing the balanced chromosomal translocation. CMA in the fetal sample did not show any significant genomic gains or losses. Thus, CMA helped us in determining the accurate prognostication of the fetus.

In case 4, amniocentesis was done in mother at 15 weeks of gestational age in view of previous child with Down syndrome. Fetal karyotype showed the presence of a de novo marker chromosome. CMA report showed five copy number state of 2.5 Mb region at 15q11.1-11.2. There were paucity of probes in pericentromeric region and 15p region. The involved region does not contain critical region of Prader-Willi/Angelman syndrome (PWS/AS) region. Hence, it may not be associated with any clinical phenotype as described by studies in the past (3). Fluorescent in situ hybridisation (FISH) using probes for 15p11.2 and 15q11.1-13 (Vysis D15ZI and GABRB3, respectively) was performed on metaphase spread. FISH report showed two extra signals for 15p11.2 regions, located on marker chromosome (Fig. 1) thus indicating the duplication of this segment also, which was not picked up by CMA. After genetic counseling, the couple decided to continue the pregnancy. Baby was followed up at 3 months and then at 1 year and was found to be normal.

In case 5, CMA identified the origin of extra chromosomal material on 12p. This implies the presence of tandem duplication of this segment.

We reported five cases where an abnormal karyotype was complemented with CMA, resulting in better delineation of the genetic defect. However, it may fail to detect origin of marker chromosome or low level mosaicism if it contains mainly heterochromatin or probe coverage in concerned area is poor. Hence along with highlighting the utility of CMA in such cases;
<table>
<thead>
<tr>
<th>S. no.</th>
<th>Age of presentation</th>
<th>Clinical features and relevant investigations</th>
<th>Antenatal and perinatal history</th>
<th>Results of karyotype and</th>
<th>Karyotype of the parents</th>
<th>CMA findings (ISCN, 2009 nomenclature)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>14 months, male</td>
<td>Global developmental delay, dysmorphism microcephaly, hypoplasia of corpus callosum, and unmyelinated peripheral white matter</td>
<td>Normal</td>
<td>46,XY,t(1;4)(q44;q27)</td>
<td>Normal</td>
<td>arr 1q43q44[24016559-249212628]X1,4q28.3(137650845-137786919)X1,17q25.3(79527879-81004770)X3 [9 Mb loss in 1q43-44,136kb loss at 4q28.3,1.4 Mb gain at 17q25.3]</td>
</tr>
<tr>
<td>3</td>
<td>9 months, female</td>
<td>Global developmental delay, facial dysmorphism, craniosynostosis, bilaterally broad and medially deviated halluces</td>
<td>Mother had oligohydramnios at 7 months of pregnancy</td>
<td>47,XX,+mar</td>
<td>Mother 46,XX,t(11;22)(q25;q13.1)</td>
<td>arr11q23.3q25(116701088-134926021)X3,22q11.1.q11.2(17073889-20728918)X3 [18 Mb gain in 11q23.3-25, 3.6 Mb gain in 22q11.1-11.2]</td>
</tr>
<tr>
<td>4</td>
<td>Prenatally at 16 weeks of pregnancy</td>
<td>Antenatal USG showed no major malformations. Child was examined at 3 months of age after birth and her development was normal</td>
<td>Normal</td>
<td>47,+marFISH for 21 chromosome – normal</td>
<td>Normal</td>
<td>arr 15q11.1.q11.2(20175623-22749949)X5 [2.5 Mb gain at 15 q, copy no −5]</td>
</tr>
</tbody>
</table>

CMA, chromosomal microarray; FISH, fluorescent in situ hybridisation; USG, ultrasonography.
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Fig. 1. Fluorescent in situ hybridisation in case 4, showing two normal copies of Prader Willi/Angelman syndrome critical region and two extra signals for 15p11.2 region on marker chromosome (white arrow).

this study also raises the importance of karyotype in conjunction with CMA.

References

3. Battaglia A. The inv dup (15) or idic (15) syndrome (Tetrasomy 15q). Orphanet J Rare Dis 2008: 3: 30.

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