Trisomy/tetrasomy 21 mosaicism in CVS: interpretation of cytogenetic discrepancies between placental and fetal chromosome complements

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Abstract
Trisomy/tetrasomy 21 mosaicism was found in chorionic villi (semidirect preparation) obtained from a 40 year old pregnant woman. Since both cell lines were abnormal, the couple elected for pregnancy termination. Placenta and fetal tissue samples were obtained for cytogenetic study. Long term cultured villi showed a non-mosaic trisomy 21 karyotype, while other tissues showed either a normal karyotype or normal/trisomy 21 mosaicism. These discrepancies could be explained by a modified “bottle neck” embryogenic model with a trisomic zygote and a non-disjunction event taking place in one of the first divisions. Our case emphasises the need for confirmatory studies in other tissues when mosaicism is encountered in chorionic villi, even if all cell lines are abnormal. (J Med Genet 1999;36:333–334)

Keywords: confined placental mosaicism; trisomy/tetrasomy 21; embryogenic models

Table 1 Cytogenetic results

<table>
<thead>
<tr>
<th>Culture type</th>
<th>No of cells</th>
<th>46,XY</th>
<th>47,XY,+21</th>
<th>48,XY,+21,+21</th>
</tr>
</thead>
<tbody>
<tr>
<td>Semidirect CVS</td>
<td>—</td>
<td>10</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Long term villi</td>
<td>—</td>
<td>8</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Cord</td>
<td>13</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Skin</td>
<td>17</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Kidney</td>
<td>64*</td>
<td>15*</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Tissue mixture</td>
<td>137*</td>
<td>44*</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

*Cells analysed by FISH.

decided to terminate the pregnancy. Termination took place at 13 weeks' gestation and placental and fetal tissue samples were obtained for cytogenetic analysis. Long term placental culture showed a non-mosaic trisomy 21 karyotype. Cord and skin cultures showed a normal karyotype in all cells examined. Other cultures established from kidney and a tissue mixture produced no metaphases and were analysed by fluorescence in situ hybridisation (FISH) using the LSI 21 Vysis probe. The mixture of nuclei with two and three signals was interpreted as a mosaic 46/47,+21 in both cultures (table 1).

Discussion
The predictive value of non-mosaic trisomy 21 found on CVS is accepted to be high.8 Only one case of a non-mosaic false positive trisomy 21 was reported in the Eucromic series of 62 865 CVS.9 However, confirmatory studies on amniocytes or fetal blood cells are recommended when a diagnosis of normal/trisomy 21 mosaicism is obtained on CVS, owing to the possibility of a normal karyotype in the fetus.

In the present case, our first interpretation was that the tetrasomic cell line was secondary to an initial trisomy 21 and probably confined to the cytotrophoblast, or, alternatively, the initial zygote could be tetrasomic and a secondary trisomic cell line had appeared in the cytotrophoblast. In either case, an abnormal fetal phenotype was assumed.

The discordance between the karyotypes obtained from the trophoblast (semidirect preparations), the chorionic mesodermal core (placenta long term culture), and the fetal tissues did not fit into the embryogenic models proposed by Crane and Cheung10 and Bianchi et al.11 These models could explain the presence of trisomic and tetrasomic cells in trophoblast, arising from an initial trisomic zygote, as well as the presence of normal cells in fetal tissues, but
not the trisomic cells found in long term placental culture and fetal tissues (fig 1A).

Kennerknecht et al proposed a modification of the embryogenic model of Crane and Cheung to explain certain fetoplacental discrepancies. According to their modified model, the cells that contribute to the inner cell mass are defined after the pluripotent eight cell stage. Following this model, we could imagine a trisomic zygote probably arising from maternal non-disjunction, and a second non-disjunction event that took place in the third mitotic division of the morula pluripotent cells, resulting in two “complementary” cell lines of 46 and 48 chromosomes, plus the initial trisomic cell line (fig 1B). By chance, the disomic cell line may have remained restricted to the inner cell mass and the tetrasomic line to the cytotrophoblast. The proportion of normal/trisomic cells in fetal tissues and extraembryonic structures can vary depending on the different cell lines.

To our knowledge, this is the first case of a discrepancy between (semi)direct CVS preparations, long term villi culture, and fetal tissues involving mosaic trisomy/tetrasomy 21. There is a reported case of a 46/48,+21,+21 mosaicism found in long term villi culture with a normal karyotype in direct preparations and in amniocytes. Hahnenmann and Vejerslev include one case of trisomy/tetrasomy 21 among autosomal tetrasomy mosaic cases, but no details were given for this particular case.

The present case emphasises the need for confirmatory studies in other fetal tissues when mosaicism is encountered in chorionic villi, even if all the cell lines are abnormal.

Funded by a grant from Fondo de Investigaciones Sanitarias (F1598/0162) to AS. The FISH studies were carried out with the aid of a grant from Fundación Catalana de la Síndrome de Down (FCSD-02).