Down’s Syndrome in Kuwait: Recurrent Familial Trisomy 21 in Sibs

S.A. Al-Awadi  K.K. Naguib  L. Bastaki  S. Gouda
F.M. Mohammed  S.J. Abulhasan  W.A. Al-Ateeqi
D.S. Krishna Murthy

Kuwait Medical Genetic Centre, Maternity Hospital, Kuwait

Abstract

Objective: To study the families with recurrent trisomy 21 in sibs, and to understand the increased risk of recurrence in some selected families. The importance of parental mosaicism as a cause for non-disjunction or the possibility of genetic predisposition to non-disjunction is addressed. Methods: Three young unrelated Kuwaiti families each confirmed to have 3 sibs with regular trisomy 21 were investigated. Detailed chromosome analysis of the peripheral blood culture in Down’s syndrome children and their parents was carried out. At least 100 cells in each of the cases were scored to exclude low grade mosaicism. Results: Regular trisomy 21 was confirmed in all the sibs in the three families. Mosaicism was not detected in parents. However, gonadal tissue mosaicism could not be excluded, as it is not practical to study the gonadal biopsy in the parents. Conclusion: Though parental mosaicism (gonadal, more often maternal), has been reported in familial recurrent trisomy 21 cases, no mosaicism could be confirmed in our study. Our finding suggests that the possibility of a genetic predisposition to non-disjunction parental mosaicism should be considered in counselling families having sibs with trisomy 21.

Introduction

Trisomy 21 is the most common aneuploidy occurring as a sporadic event with a frequency of 1 in 600–800 live births [1, 2]. Down’s syndrome due to primary trisomy 21 in 2 or more sibs of healthy, normal young parents (<30 years) occurs rarely. Although the recurrence of trisomy 21 is 1–2% for young mothers after the first case [3, 4], there
### Table 1. The characteristic features of the three families with recurrent trisomy 21

<table>
<thead>
<tr>
<th>Family</th>
<th>Age of child years</th>
<th>Sex</th>
<th>Nationality</th>
<th>Maternal age</th>
<th>Paternal age</th>
<th>Consanguinity</th>
<th>Birth order</th>
<th>Presentation</th>
<th>Gestation</th>
<th>Mode of delivery</th>
<th>Patient karyotyping</th>
<th>Affected relatives</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>13</td>
<td>female</td>
<td>Kuwaiti</td>
<td>25</td>
<td>30</td>
<td>less than second cousin</td>
<td>3</td>
<td>cephalic</td>
<td>term</td>
<td>spontaneous</td>
<td>47,XX, +21</td>
<td>2</td>
</tr>
<tr>
<td>II</td>
<td>10</td>
<td>induced abortion</td>
<td>Kuwaiti</td>
<td>28</td>
<td>33</td>
<td>second cousin</td>
<td>4</td>
<td>cephalic</td>
<td>term</td>
<td>spontaneous</td>
<td>47,XX, +21</td>
<td>0</td>
</tr>
<tr>
<td>III</td>
<td>10</td>
<td>male</td>
<td>non-Kuwaiti</td>
<td>33</td>
<td>33</td>
<td>non-consanguinity</td>
<td>6</td>
<td>cephalic</td>
<td>term</td>
<td>spontaneous</td>
<td>47,XX, +21</td>
<td>0</td>
</tr>
</tbody>
</table>

- **Sex**: female, male
- **Nationality**: Kuwaiti, non-Kuwaiti
- **Consanguinity**: less than second cousin, second cousin, non-consanguinity
- **Birth order**: 3, 4, 6, 4, 5, 7, 2, 3, 4
- **Presentation**: cephalic, cephalic, cephalic, cephalic, cephalic, cephalic, cephalic, cephalic, cephalic
- **Gestation**: term, term, 13 weeks, term, term, term, term, term, term
- **Mode of delivery**: spontaneous, spontaneous, spontaneous, spontaneous, spontaneous, spontaneous, spontaneous, spontaneous, spontaneous
- **Patient karyotyping**: 47,XX, +21, 47,XX, +21, 47,XY, +21, 48,XXY, +21, 47,XY, +21, 47,XY, +21, 47,XY, +21, 47,XY, +21

<table>
<thead>
<tr>
<th>Affected relatives</th>
<th>Maternal karyotyping</th>
<th>Paternal karyotyping</th>
<th>Satellite association</th>
<th>Tissue culture</th>
<th>Associated anomalies</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>46,XX</td>
<td>46,XY</td>
<td>high (55%)</td>
<td>46,XY, 16qh+</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>not tested</td>
<td>46,XY</td>
<td>imperforated anus</td>
</tr>
</tbody>
</table>

No figures for the risk of multiple recurrence of trisomy 21 or other aneuploidy in young parents, but there are several reports suggesting that the probability is greater than expected. The aetiology of familial non-disjunction is not well established. There are several possible explanations for familial occurrence of aneuploidy. The first of these is cryptic parental mosaicism [5–9]. The other possibility is ‘genetic predisposition’, as suggested by Alfi et al. [10] and others [11–13]. Whatever the cause, counselling young parents with 2 or more sibs with trisomy 21 poses difficulties.

We report here recurrent trisomy in three families, each of them having 3 sibs with primary trisomy 21, and a brief review of families with 3 or more cases of trisomy 21 reported in the literature, speculating on its possible aetiology.
Materials and Methods

Three unrelated Kuwaiti families each with 3 Down’s syndrome sibs were ascertained, clinically and cytogenetically. The clinical history of the three families is presented in table 1 and figures 1 and 2.

Family I

The proband is a female infant, the product of the 4th pregnancy to consanguineous (less than first cousin) phenotypically normal parents. At birth, the parental ages were 23 and 28 years for the mother and father, respectively. Preconceptional and first trimester histories were unremarkable. At birth the baby showed the clinical stigmata of Down’s syndrome. Pedigree study revealed that the proband has 2 elder phenotypically normal female sibs, 2 younger phenotypically normal sibs (brother and sister; fig. 1), 1 elder female sib with Down’s syndrome and 1 early spontaneous abortion. Four years later the proband’s mother conceived and prenatal diagnosis using transabdominal microvillus sampling technique revealed a regular trisomy 21 fetus, subsequently terminated.

Family II

The proband is a non-Kuwaiti male neonate, the product of the 7th pregnancy to his consanguineous (second cousin) phenotypically normal parents. At birth the parental age was 40 years for both parents. Preconceptional, first and second trimester histories were unremarkable. A healthy normal male child was delivered at term by vaginal delivery with an average birth weight. On examination at birth he showed the typical features of Down’s syndrome. His 2 elder brothers showed clinical features of Down’s syndrome with regular trisomy 21 cytogenetically. Interestingly, although 1 of the children had double aneuploidy 48,XXY,+21, he presented with clinical features of Down’s syndrome.

Family III

The proband, a Kuwaiti male neonate, the result of the 3rd pregnancy to his non-consanguineous phenotypically normal parents. At birth parental ages were 23 and 28 years for both his mother and father, respectively. Preconceptional, first and second trimester histories were unremarkable and the pregnancy ended at...
term by spontaneous vaginal delivery. Pedigree study revealed that the proband had 2 elder male sibs, 1 of whom was similarly affected, and subsequently the proband’s mother delivered a male child who also showed clinical features of Down’s syndrome.

**Cytogenetic Studies**

Cytogenetic analysis in all the sibs and parents of the three families were carried out using peripheral blood lymphocyte culture and Giemsa trypsin banding technique. A minimum of 20 metaphases were scored and 3–5 cells were karyotyped in each case. In order to exclude mosaicism, 50–100 cells were scored. Mosaicism was not detected in the parents of the three families in the peripheral blood cultures. However, the possibility of tissue-specific mosaicism (gonadal) cannot be excluded.

**Discussion**

The presence of 2 or more sibs affected with a chromosome abnormality may suggest the existence of a familial factor leading to an error in chromosome segregation in families having multiple members with aneuploidy [14–16], i.e., a genetic susceptibility to nondisjunction. Mosaicism in man may be under genetic control as has been shown in maize and drosophila. However, the presence of trisomy 21 in multiple sibs may be either due to mosaicism in one of the parents or an inherited predisposition [17]. The prevalence of

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Fig. 2. Pedigree of families II and III showing trisomy 21 in 3 male sibs and parental consanguinity in family II.
Table 2. Recurrent trisomy 21 in sibs: summary of reported cases

<table>
<thead>
<tr>
<th>Family No.</th>
<th>Sibs with trisomy 21</th>
<th>Parental age</th>
<th>Mosaicism</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>maternal</td>
<td>paternal</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>3</td>
<td>25, 28, 29</td>
<td>–</td>
<td>+</td>
</tr>
<tr>
<td>2</td>
<td>3^</td>
<td>30–32</td>
<td>29–31</td>
<td>–</td>
</tr>
<tr>
<td>3</td>
<td>3</td>
<td>19–32</td>
<td>–</td>
<td>+</td>
</tr>
<tr>
<td>4</td>
<td>3</td>
<td>22–24</td>
<td>–</td>
<td>+</td>
</tr>
<tr>
<td>5</td>
<td>3</td>
<td>–</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>3</td>
<td>24, 27, 29</td>
<td>–</td>
<td>+</td>
</tr>
<tr>
<td>7</td>
<td>4</td>
<td>17, 19, 21, 25</td>
<td>36, 38, 39</td>
<td>–</td>
</tr>
<tr>
<td>8</td>
<td>3</td>
<td>25, 28, 29</td>
<td>–</td>
<td>+</td>
</tr>
<tr>
<td>9</td>
<td>3</td>
<td>–</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>3</td>
<td>27, 29, 31</td>
<td>29, 32, 33</td>
<td>+</td>
</tr>
<tr>
<td>11</td>
<td>3</td>
<td>25, 26, 34</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>12</td>
<td>6</td>
<td>23–30</td>
<td>26–33</td>
<td>+</td>
</tr>
<tr>
<td>13</td>
<td>4</td>
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<tr>
<td>14</td>
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<td>25, 30, 36</td>
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<tr>
<td>15</td>
<td>3</td>
<td>&lt;30</td>
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<td>–</td>
</tr>
<tr>
<td>16</td>
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<td>22, 23, 27</td>
<td>39, 40, 44</td>
<td>+</td>
</tr>
<tr>
<td>17</td>
<td>3</td>
<td>19, 25, 29</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>18</td>
<td>3</td>
<td>18, 19, 26</td>
<td>22, 23, 30</td>
<td>+</td>
</tr>
<tr>
<td>19</td>
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<td>3</td>
<td>21–43</td>
<td>32–49</td>
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<td>24</td>
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<td>+</td>
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<td>33, 36, 40</td>
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</tr>
<tr>
<td>23</td>
<td>3</td>
<td>22, 23, 32</td>
<td>29, 30, 39</td>
<td>–</td>
</tr>
</tbody>
</table>

Mosaicism: + = present; – = absent.

^ This family was reinvestigated by Uchida and Freeman [34]. Maternal mosaicism was confirmed in 2% of the cells. Mosaicism: 47,XX,+21 in ovarian tissue (100%).

Chromosome 21 mosaicism in a random normal population is not known in most newborn surveys because large numbers of cells are not scored to exclude low grade mosaicism. Very few authors agree with the existence of a single-gene hypothesis [10, 18, 19]. However, other authors reported no evidence to support the suggestion of an inbreeding effect [12, 20–25]. In the literature very few reports describe Down’s syndrome in sibs (table 2), but some authors found maternal mosaicism as the underlying cause for recurrent Down’s syndrome [29, 31, 44]. On the other hand, Bartsch et al. [45] described a Spanish family who had 2 sibs with dup (21q) Down’s syndrome whose mother has three different chromosome anomalies: a chromosome 22 with an unusual pericentromeric region that contains alphoid DNA from chromosome 21/13 and chromosome 22, an isochromosome 21p, and an isochromosome 21q in a rare second cell line.

In the present study, we report three families with 3 sibs having regular trisomy 21, in addition to nine other families who had 2 sibs with regular trisomy 21 Down’s syndrome.
who were recorded among the 1,650 families with 1 Down’s syndrome registered in Kuwait making a prevalence rate of 7.3/1,000 Down’s patients. This recurrent rate of familial Down’s syndrome is higher than the expected prevalence in a highly inbred population like Kuwaitis where the incidence of consanguinity is estimated to be 54.3% [46]. However, this rate does fit with the high incidence rate of Down’s syndrome registered in Kuwait where the incidence rate was estimated to be 4/1,000 live births [unpublished data]. This finding necessitates the need to correct the figures of estimated recurrence risk after the 1st Down’s syndrome patient in the general Kuwaiti population from 2.6/1,000 to 8/1,000 births. This new estimate is based on the new incidence figure of Down’s syndrome registered in Kuwait. After the 2nd Down’s syndrome child the estimated recurrence risk will be as high as 30%.

Cytogenetically, neither mosaicism nor cytogenetic abnormality were found in any of the parents. Mosaicism cannot be excluded completely, particularly in the gonadal tissues of the parents. Accordingly, if we refer to the assumed genetic factor and consider it as a single recessive gene, one would expect multiplex families to be more prevalent especially in a highly inbred population like the Kuwaiti population. A similar finding was concluded by Basaran et al. [23]. The authors recorded 20 cases of Down’s syndrome in sibs out of a population of 1,598 making a prevalence rate of 12.5/1,000 Down’s patients. These findings together with our findings do not support the contribution of an autosomal recessive gene to the aetiology of non-disjunction, especially in highly inbred populations. Such a mechanism has not been assumed for other trisomies and it is unlikely that aneuploidy genes would preferentially affect chromosome 21.

Non-disjunction could possibly be attributed to genetic, environmental or a combination of the two factors. Theoretically genes predisposing to increased non-disjunction can be classified in several different ways: (a) gene(s) resulting in non-disjunction of a specific chromosome (e.g. chromosome 21)-homoaneuploidy, (b) gene(s) that can predispose non-disjunction of different autosome/sex chromosome in the same individual, or in sibs, due to parental and/or postzygotic non-disjunction-heteroaneuploidy (e.g. 48,XX, or XY,+21,+18; 48,XXY,+21 46,X,-X,+21). The occurrence of ‘heteroaneuploidy’ would not prove the existence of predisposition gene(s). Such outcome may be carried by parental mosaicism which has been demonstrated in some families with >2 trisomy 21 sibs. Familial ‘heteroaneuploidy’ is very rare. However, the occurrence of aneuploidy for different chromosomes is a better evidence for genetic predisposition although environmental factors could also be invoked as a possible cause. Amniocentesis and live birth data provided little evidence for a strong ‘heteroaneuploidy effect’ although a weak effect cannot be excluded. Studies in abortions are suggestive of genetic mosaicism of heteroaneuploidy [25].

In conclusion, non-disjunction could be possibly attributed to genetic, environmental or combined factors. Unfortunately, the nature of the mechanism of the genetic factor is yet to be revealed. The single-gene hypothesis is not yet accepted and even if accepted it must be limited to very specific situations. A hidden low grade mosaicism in one of the parents’ blood or gonadal mosaicism may be the underlying cause and is not absolutely excluded in this report. Further investigations for all families including cytogenetic, FISH and DNA studies are highly recommended and will be arranged in the near future. The present report strongly supports that a subgroup of Down’s syndrome families are at increased risk of recurrence.
References


30. Belegltter et al: Cited from Frohlich et al [32].


