Mental retardation: diagnostic studies on aetiology
van Karnebeek, C.D.

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Chapter

Pilot study: Screening for subtelomeric rearrangements in mental retardation

CDM van Karnebeek\textsuperscript{1,2}
S Sluijter\textsuperscript{1}
EK Bijlsma\textsuperscript{1}
RCM Hennekam\textsuperscript{1,2}
JMN Hoovers\textsuperscript{1}

\textsuperscript{1} Department of Clinical Genetics;
\textsuperscript{2} Department of Paediatrics/Emma Children’s Hospital;
Academic Medical Centre, Amsterdam, The Netherlands

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Prompted by Flint et al (1995), we performed a pilot study to investigate the presence of subtelomeric rearrangements in a highly biased group of cases with MR, all suspected to have a chromosome anomaly.

Thirty paediatric and adult patients (17m:13f), all evaluated in the Department of Clinical Genetics of our institution, were retrospectively included in the study cohort if they fulfilled the following criteria: presence of MR; no known aetiological diagnosis; a normal karyotype at a 550 G-band level; and one or more of: presence of dysmorphic features suggestive to the clinical geneticists (EB; RH) for a chromosome anomaly; family history positive for MR; multiple unexplained miscarriages within the same sibship. All subtelomeric regions were screened by standard FISH analysis using probes (P1 clones for chromosome arms 2q, 4q, 6q, 9q, 11q, 17p, 18p, 18q, 22q) described by Vocero-Akbani et al (1996), clone for 11pter described by Russel et al (1996), and all other subtelomeric clones by NIH and IMM Collaboration (1996).

A subtle chromosome rearrangement involving the telomeres was detected in 5 patients (16.7%). Their karyotypes are listed in Table 1, and their respective case summaries below.

Table 1. Subtelomeric chromosome anomalies detected in the pilot study

<table>
<thead>
<tr>
<th>Karyotype</th>
<th>Origin</th>
</tr>
</thead>
<tbody>
<tr>
<td>46,XX ish der(4)t(4;7)(q35;p22.3)</td>
<td>unknown</td>
</tr>
<tr>
<td>46,XX ish der(14)q32.31</td>
<td>de novo</td>
</tr>
<tr>
<td>46,XX ish del(2)(q37 3</td>
<td>de novo</td>
</tr>
<tr>
<td>46,XX ish del(2)t(2;6)(q37 3;p25)</td>
<td>maternal</td>
</tr>
<tr>
<td>46,XX ish del(4)p16 3</td>
<td>de novo</td>
</tr>
</tbody>
</table>

Case 1

During pregnancy mother had been in contact with Rubella, without being vaccinated or having had Rubella herself. She was born at term with a normal birth weight. There was no cataract, hearing loss or heart defect. Developmental delay became apparent in early childhood. She was severely mentally retarded necessitating placement in an institute for the mentally handicapped. She had no speech. She died at the age of 30 years. Physical examination showed a head circumference of 58 cm (P90), hypertelorism, prominent eyebrows, a small nose with a low nasal bridge. There were no internal anomalies.
Case 2
This female is described in more detail by Van Karnebeek et al. (2002) in Chapter 3. She shows many features typical of the terminal 14q deletion syndrome: mental retardation, hypotonia, high forehead, narrow bifrontal diameter, blepharophimosis, epicanthi, asymmetrical ptosis, a broad and flat nasal bridge, bulbous nose with upturned nares, long and broad philtrum, malformed helices, mild micrognathia, and a unilateral palmar crease.

Case 3
This female is described in more detail by Bijlsma et al. (1999). Next to a family history positive for multiple congenital anomalies in 2nd and 3rd degree relatives, she had a long, asymmetric face with sparse eyebrows, prominent forehead, bilateral epicanthal folds, coloboma of the alae nasi with prominent columella, and a small mouth. She had a bilateral single palmar crease.

Case 4
The first pregnancy of the healthy, non-consanguineous parents of this patient ended in an intra-uterine demise at 6 months. The eldest sister is moderately retarded and has mild dysmorphic facial features and a scoliosis; the second sister has a normal development and pulmonary stenosis. This female is third and youngest daughter, born after an uneventful term pregnancy. She is severely retarded and suffers bilateral cataracts. Other phenotypic features include: hypertelorism, shallow orbits, high palate, thick tongue, short philtrum, micrognathia, low set ears, short broad hands with short fifth fingers. At age 8 years, orthopedic surgery was performed for severe scoliosis. She developed severe contractures and died at the age of 14 years 6 months, shortly after a second scoliosis correction. The unbalanced karyotype of this patient (dup 2qter/del 6pter) was a result of a balanced cryptic rearrangement between 2qter and 6pter in mother. As expected, the eldest patient carried the other unbalanced karyotype (del 2qter.dup 6pter), while the second daughter has a normal karyotype.

Case 5
The proband was born after an uneventful pregnancy of 38 5/7 weeks, birth weight being 2330 gram, length was 46 cm, and OFC was 33 cm (all <P3). She was the first child of a healthy, non-consanguineous couple. Immediately after birth she had respiratory problems for which she was admitted to a neonatal intensive care unit. Echocardiography showed an atrial septum defect type II. She had prolonged feeding problems. Growth and development were severely delayed. Physical examination at 1 year showed a sloping forehead, hypertelorism, large and round eyes, strabismus, flat malae, high nasal bridge, small mouth, tented upper lip, small cleft of the soft palate, and a branchial cyst. She had long slender fingers and toes. The findings were suggestive of the 4p- (Wolf-Hirschhorn) syndrome.
The results of the present study allowed us to conclude that also in our hands FISH analysis is a valid technique for detecting subtelomeric rearrangements. The frequency and nature of the detected microdeletions in this study group is similar to those in other, comparable studies. This is probably due to an introduced bias in favour of cases more likely to have a chromosome anomaly, such as familial cases with MR or cases with a suspect "chromosomal phenotype", which is similar to other studies.\textsuperscript{7,10} Little is known therefore of the true prevalence of subtelomeric rearrangements in MR, which motivated us to perform a prospective screening study in an unselected group of children with unexplained MR (see Chapter 5).\textsuperscript{11}
