Mild phenotypic manifestation of a 7p15.3p21.2 deletion

C Wang, S Maynard, T W Glover, L G Biesecker

Abstract
A 28 month old girl with dysmorphic features was found to have an interstitial deletion of the short arm of chromosome 7p15.3-7p21.2. The patient had ptosis, dacyrystenosis, pectus excavatum, short hands, and her development was normal or mildly delayed. Craniosynostosis and growth retardation, which were present in two other patients with similar deletions, were not present. Because of the mild manifestations, this case expands the clinical spectrum of the 7p15-7p21 deletion phenotype.

Numerous patients with interstitial and terminal deletions of 7p have been described and the patients in this group are diverse in their morphological, degree of developmental delay, and growth characteristics.1 A subset of this group includes two patients with deletions limited to 7p15p21.23 These patients manifested craniosynostosis, mental and growth retardation, and craniofacial anomalies. We report a child with dysmorphic features without major anomalies or marked growth or developmental delay who has a deletion of 7p15.3p21.2. This case expands the phenotypic spectrum of 7p− syndrome and contributes to the localisation of the 7p craniosynostosis locus.

Case report
The proband was 28 months old at the time of her most recent genetics evaluation. She was born to a 31 year old, gravida 2, para 2 woman after an uncomplicated 42 week gestation. Her father was 34 years of age at the time of her delivery. Her birth weight was 4300 g, and birth length was 53.3 cm. During the first few months of life she was noted to have ptosis with dacyrystenosis and conjunctivitis. She also had several ear infections during these first few months. A heart murmur was diagnosed at the age of 4 months, and an echocardiogram was interpreted as suggestive of a small atrial septal defect. She was also noted to have an umbilical hernia that later spontaneously reduced. She sat at 6 to 7 months of age and walked at 13 months of age. At 16 months of age she used three to four words but by two years of age the parents began to suspect a delay in expressive speech.

The patient has a 6 year old sib and a 15 year old half sib who are normal. Her parents are healthy with the exception of endometriosis in her mother.

Physical examination showed her height to be 88 cm (50th centile), weight 13.2 kg (50th to 75th centile), and head circumference 46.8 cm (approximately 2nd centile). Her hair texture and distribution and head configuration were normal. The ears were normally placed but posteriorly rotated. She had downward slanting palpebral fissures with bilateral epicanthic folds and prominent eyelashes (fig 1). Marked ptosis was present bilaterally. A grade 1/6 systolic murmur was noted at the left midsternal border. Mild pectus excavatum was present. The fingers appeared short overall, most obvious in the distal phalanges, and the thumb was proximally placed. The feet were unremarkable with the exception of broad hallucs. The neurological examination was normal.

A skeletal survey showed a bone age of 15 to 18 months at a chronological age of 17 months. A pattern profile analysis6 indicated that the proximal fifth phalanges and distal phalanges of all digits were more than 1.5 SD below the mean (fig 2). No evidence of craniosynostosis was present on skull radiographs. A routine metaphase chromosome analysis of peripheral blood lymphocytes showed a possible interstitial deletion of 7p15−7p21. A repeat study with prophage analysis (850 bands) showed a karyotype of 46,XX,del(7)(p15.3p21.2) in 20 of 20 cells counted (fig 3). Prophage chromosome analyses of both parents were normal. An auditory evaluation indicated a mild conductive loss with serous effusions. A Gesell de-
velopmental screening test performed at 4
years 8 months indicated an overall age equi-
valent performance of 4 years (subtest range of
3½ to 4½ years.)

Discussion
The features of our patient and two previously
described patients23 with similar deletions are
summarised in the table. All three patients had
posteriorly rotated ears and ptosis. Two of
three patients had downward slanting palpe-
bral fissures, proptosis, short nose, small
jaw, pectus excavatum, short fingers, simian
creases, and growth and developmental delay.
It is remarkable that the patient reported here
apparently has, at most, mild retardation of
development and several of the subtests are
normal for age. The Gesell developmental
resulting test would predict that this patient
would perform in the low average normal
range of intellectual functioning with an IQ of
80 to 90. The patient described by Garcia-
Esquivel et al22 had severe growth and mental
retardation (7p15.2–p21.2) while the patient
described by Motegi et al22 was mild to moder-
ate in these manifestations (7p15.3–p21.3).

Figure 2 Pattern profile analysis of the right hand of
the patient. The pattern profile analysis confirms the
clinical finding of shortened phalanges and shows that
the most severe shortening is in the distal phalanges.

Figure 3 The normal and p15.3–21.2 deleted short arms of chromosome 7. The
diagram shows the estimates of the breakpoints and is flanked by photographs of the
corresponding chromosomes.

The present patient expands the spectrum of this
deletion because of the mild nature of her
phenotype. We were impressed with the
shortened phalanges in our case (fig 2).
Shortening of the hands was noted in the case
of Motegi et al22 and in previous cases of 7p-
with larger deletions.15–12 Hinkel et al22 reported
two patients with 7p deletions (7p13–p15 and
7p13–pter), both of whom had shortening of the
digits. This would suggest that the digital
abnormality is related either to the pathophys-
iology of craniosynostosis or is connected
with another locus on 7p. The existence of a
number of acrocephalosyndactyly syndromes
that are apparently monogenic could support
the notion that a single gene could cause
abnormal growth of cranial and digital epi-
physes.

The presence or absence of craniosynostosis
has been the most widely discussed clinical
finding in patients with deletions in this re-
gion.11 While most cases support the notion of
a craniosynostosis locus being within the
7p21–22 region (CRS1), further delineation of
the locus has been difficult to accomplish.
Fryns et al12 proposed that del(7p22) alone would
result in premature closure of the cranial suture.
Accurate assessment of phenotype–
genotype correlations is hampered by the fact
that most of the cytogenetic analyses were
performed without high resolution techniques.
However, the more recent reports with high
resolution analysis22 suggest subbands 7p21.1
or 7p21.2 as the likely distal 7p synostosis
locus. The absence of craniosynostosis in the
present case would suggest that the locus is in
the telomeric portion of 7p21.2. Brueton et al13
have described patients with craniosynostosis
and 7p deletions evaluated with molecular
probes and the data suggest CRS1 is in 7p21.
Aughton et al14 and Hinkel et al12 have recently
described patients with craniosynostosis and
more proximal 7p deletions (7p11.2–7p14 and
7p13–7p15, respectively). They concluded that
there must be a second synostosis locus on
7p distinct from that found in 7p21. This
second locus has been designated CRS2 by
Brueton et al.13

The present patient is similar to the two
other 7p15p21 deletion patients but also has a
number of significant differences (table). Al-
though the craniofacial and limb findings are
similar in these three patients, there are sig-
ficant differences in growth and development
as well as some of the dysmorphic features. It
would be difficult to provide accurate progno-
sic information if such a deletion were detected
pre- or neonatally given the marked hetero-
genecity among the patients. More exact
delineation of genotype–phenotype correlation
will await the description of additional patients
with high resolution chromosome studies and
deletion analysis with DNA markers.

The authors thank Janice LaPointe, Ann
McCarten, and Lynda Pancratz for word pro-
cessing assistance. M Michael Cohen assisted
with interpretation of radiographs and review
of published reports. Dr Frank Jung translated
the Hinkel et al reference.
<table>
<thead>
<tr>
<th>Phenotypic Features</th>
<th>Garcia-Esquival et al&lt;sup&gt;1&lt;/sup&gt;</th>
<th>Motegi et al&lt;sup&gt;3&lt;/sup&gt;</th>
<th>Present case</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deletion</td>
<td>p15.2p21.2</td>
<td>p15.3p21.3</td>
<td>p15.3p21.2</td>
</tr>
<tr>
<td>Mental retardation</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Synostosis</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Height &lt; 5th centile</td>
<td>+</td>
<td>+/-</td>
<td>+/-</td>
</tr>
<tr>
<td>Weight &lt; 5th centile</td>
<td>+</td>
<td>+/-</td>
<td>+/-</td>
</tr>
<tr>
<td>OFC &lt; 2nd centile</td>
<td>+</td>
<td>+/-</td>
<td>+/-</td>
</tr>
<tr>
<td>Ears</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Posterior rotation</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Size</td>
<td>Hypoplastic lobules</td>
<td>Small</td>
<td>Large helix</td>
</tr>
<tr>
<td>Eyes</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Interorbital distance</td>
<td>Decreased</td>
<td>Increased</td>
<td>Normal</td>
</tr>
<tr>
<td>Epicanthic folds</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Palpebral fissures</td>
<td>Upward slanting</td>
<td>Downward slanting</td>
<td>Downward slanting</td>
</tr>
<tr>
<td>Proptosis</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Strabismus</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Nose</td>
<td>Anteverted</td>
<td>Large, blunt tip</td>
<td>Depressed bridge</td>
</tr>
<tr>
<td>Length</td>
<td>Short</td>
<td>Short</td>
<td>+</td>
</tr>
<tr>
<td>Mouth</td>
<td>Retragnathia</td>
<td>Micrognathia</td>
<td></td>
</tr>
<tr>
<td>Chest</td>
<td>Widely spaced nipples</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Genitalia</td>
<td>Hypoplasia, cryptorchidism</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Limbs</td>
<td>Hand structure</td>
<td>Campodactyly</td>
<td>Sydactyly</td>
</tr>
<tr>
<td>Ridge count</td>
<td>+</td>
<td>Absent</td>
<td>Decreased</td>
</tr>
<tr>
<td>Simian crease</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
</tbody>
</table>

= absent; + = mild; ++ = moderate.