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

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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, dacryostenosis, 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.

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Numerous patients with interstitial and terminal deletions of 7p have been described and the patients in this group are diverse in their morphology, degree of developmental delay, and growth characteristics.[1] A subset of this group includes two patients with deletions limited to 7p15p21.[2,3] 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 dacryostenosis 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 halluces. 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 analysis[4] 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 prophase analysis (850 bands) showed a karyotype of 46,XX,del(7)(p15.3p21.2) in 20 of 20 cells counted (fig 3). Prophase chromosome analyses of both parents were normal. An auditory evaluation indicated a mild conductive loss with serous effusions. A Gesell de-

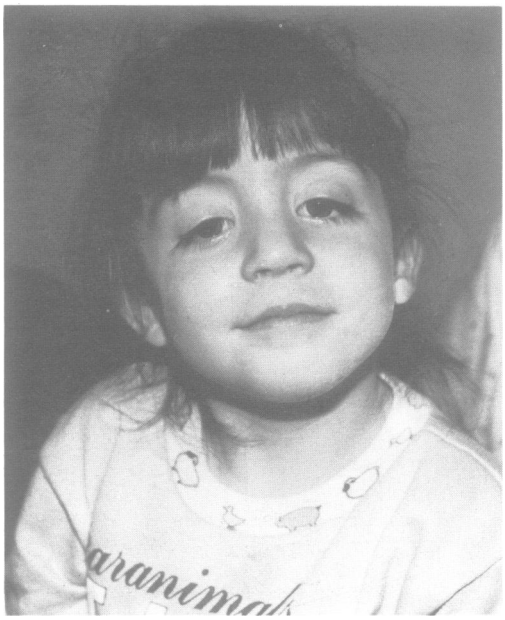

Figure 1 The craniofacial features of the patient include epicanthic folds, prominent eyelashes, downward slanting palpebral fissures, and ptosis.

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velopmental screening test performed at 4 years 8 months indicated an overall age equivalent performance of 4 years (subtest range of $3\frac{1}{2}$ to $4\frac{1}{2}$ years.)

Discussion

The features of our patient and two previously described patients[2 3] with similar deletions are summarised in the table. All three patients had posteriorly rotated ears and ptosis. Two of three patients had downward slanting palpebral 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 testing result 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 al*[2] had severe growth and mental retardation (7p15.2–p21.2) while the patient described by Motegi *et al*[3] was mild to moderate in these manifestations (7p15.3–p21.3).

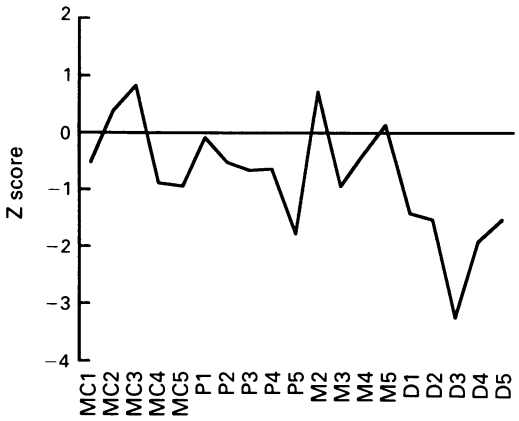

Figure 2 Pattern profile analysis of the right hand of the patient. The pattern profile analysis confirms the clinical finding of shortened phalanges and shows that the most severe shortening is in the distal phalanges.

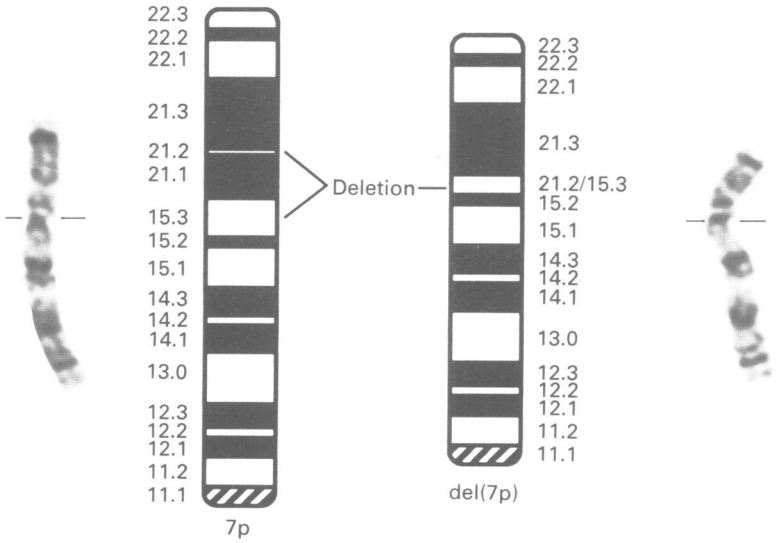

Figure 3 The normal and p15.3–21.2 deleted short arms of chromosome 7. The diagram shows the estimates of the breakpoints and is flanked by photographs of the corresponding chromosomes.

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 al*[3] and in previous cases of 7p- with larger deletions.[1 5–12] Hinkel *et al*[6] 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 pathophysiology of craniosynostosis or is connected with another locus on 7p. The existence of a number of acrocephalosyndactyly syndromes that are apparently monogenic[12] would support the notion that a single gene could cause abnormal growth of cranial and digital epiphyses.

The presence or absence of craniosynostosis has been the most widely discussed clinical finding in patients with deletions in this region.[1 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 al*[11] proposed that del(7p22) alone will result in premature closure of the cranial sutures. 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 analysis[2 3] 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 al*[13] have described patients with craniosynostosis and 7p deletions evaluated with molecular probes and the data suggest *CRS1* is in 7p21. Aughton *et al*[14] and Hinkel *et al*[6] 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). Although the craniofacial and limb findings are similar in these three patients, there are significant differences in growth and development as well as some of the dysmorphic features. It would be difficult to provide accurate prognostic information if such a deletion were detected pre- or neonatally given the marked heterogeneity among the three 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.

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Comparison of phenotypic features in 7p- microdeletion patients.

	Garcia-Esquival *et al*[2]	Motegi *et al*[3]	Present case
Deletion	p15.2p21.2	p15.3p21.3	p15.3p21.2
Mental retardation	+ +	+	−
Synostosis	+	+	−
Height < 5th centile	+	−	−
Weight < 5th centile	+	+/−	−
OFC < 2nd centile	+	−	+/−
Ears			
Posterior rotation	+	+	+
Size		Small	Large helix
Hypoplastic lobules		+	
Eyes			
Ptosis	+	+	+
Interorbital distance	Decreased	Increased	Normal
Epicanthic folds	+		+
Palpebral fissures	Upward slanting	Downward slanting	Downward slanting
Proptosis	+	+	
Strabismus	+		
Nose	Anteverted	Large, blunt tip	Depressed bridge
Length	Short	Short	
Mouth	Retrognathia	Micrognathia	
Chest			
Pectus excavatum	+		+
Widely spaced nipples	+		
Genitalia	Hypoplasia, cryptorchidism		
Limbs			
Hand structure	Camptodactyly Syndactyly		Brachydactyly
Ridge count		Absent	Decreased
Simian crease	+	+	

− = absent; + = mild; + + = moderate.

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