J. Wang · L. Spitz · R. Hayward · E. Kiely · C. M. Hall · D. P. O’Donoghue
R. Palmer · F. R. Goodman · P. J. Scambler · R. M. Winter · W. Reardon

Sacral dysgenesis associated with terminal deletion of chromosome 7q: a report of two families

Received: 4 February 1999 / Accepted: 27 April 1999

Abstract Most cases of sacral dysgenesis are considered to be sporadic events. We present two families in whom the presence of associated clinical features prompted specific investigation of chromosome 7, leading to the identification of an underlying chromosome 7q deletion causing sacral dysgenesis. All affected individuals had microcephaly and developmental delay. Detailed cytogenetic studies confirmed that all three affected individuals had a deletion of chromosome 7q associated with their sacral dysgenesis, developmental delay and related problems. The three affected patients were studied clinically, radiologically and cytogenetically. Eleven unaffected individuals from the two families were also investigated by genetic studies, specifically evaluating chromosome 7.

Conclusion It is important that detailed family history, evaluation of associated malformations and the overall clinical picture be considered in identifying the underlying diagnosis in cases of anal stenosis/sacral agenesis. The cases we present demonstrate the value of detailed chromosome studies in such situations.

Key words Sacral dysgenesis · Anal stenosis · Currarino syndrome · Chromosome

Introduction

Sacral malformation is usually a sporadic event and, once maternal diabetes has been excluded, the recurrence risk within a family is small [4]. Unless there is an associated clinical problem, such as an imperforate anus, sacral malformations frequently remain undiagnosed. This has been well documented in several individuals with Currarino syndrome, an autosomal dominant form of sacral dysgenesis, which, in the complete form, is associated with anorectal atresia and a presacral mass, either meningocele, enteric cyst or benign teratoma [2]. Typically the sacral malformation of Currarino syndrome is described as a sickle shaped hemisacrum, but the presence of this malformation has been shown to be variable within affected families [15]. Although Currarino syndrome is likely to represent only about 5% of symptomatic patients with anorectal malformations, the involvement of the urogenital system and the lower gastro-intestinal tract is very similar to that observed with sporadically occurring sacral dysgenesis [7]. Likewise the very significant morbidity and mortality attending symptomatic sacral malformation applies to both familial and sporadically occurring patients [10, 16,
These studies emphasise that anorectal and sacral malformations occurring in the same patient are unlikely to be random events and that many such cases may represent new mutations at the Currarino syndrome locus. Consequently it is reasonable to speculate that identification of the genetic basis of Currarino syndrome is likely to also benefit a group of patients with a wider spectrum of sacral anomalies than those with this form of sacral dysgenesis only.

The gene for Currarino syndrome having been mapped to chromosome 7q [11], has recently been established as a homeobox gene, \textit{HLXB9} and several mutations have been published [17]. The initial mapping, which has based on a linkage approach in two well characterised families, was aided by case reports establishing an association between monosomy 7q36 and sacral agenesis with and without holoprosencephaly [13, 21]. We now report patients from two families, presenting initially with anorectal stenosis, in whom exploitation of advanced techniques of chromosome analysis combined with the knowledge that a gene for sacral malformation lies at the tip of chromosome 7q enabled an underlying genetic diagnosis to be established as the basis of the surgical problem in both instances.

### Case reports

#### Case 1

A 10-year-old girl was referred to hospital because of sacral dysgenesis. She was born to a 27-year-old primagravida at 34 weeks gestation by Caesarean section for fulminating pre-eclampsia. Initially she was well for 3 weeks and then developed severe enterocolitis which was positive to clostridial toxin. This responded to medical treatment but she developed recurrence of symptoms with gross abdominal distension. Rectal examination showed evidence of a narrow constriction ring in the anal canal with a rectovaginal fistula. A double-barrelled colostomy was formed at day 53 and the subsequent post-operative course was complicated by recurrent wound problems. She required long-term antibiotics and parenteral nutrition. At 9 months of age she had a Soave pull-through procedure. Faecal incontinence persisted and she also has a neuropathic bladder for which intermittent catheterisation is required.

Sacral dysgenesis was diagnosed at 5 years of age. A radiograph of the lumbosacral spine showed only three lumbar vertebral segments and an exceptionally short sacrum (Fig. 1). One year later, she presented with foot weakness. MRI demonstrated that the caudal end of the spinal cord was low and ended in a lipomatous mass in the sacral canal. The sacrum itself appeared hypoplastic with only two segments. A spinal de-tethering operation was undertaken and the mass was excised. The histological features were those of fibrofatty tissue.

In addition to these specific problems, she is below the 3rd percentile for height and weight and has microcephaly with a marked degree of hypotelorism. She is significantly delayed developmentally, attending a school for children with moderate learning difficulties and has had a number of seizures.

#### Cytogenetic findings

Initial chromosomal analysis was normal but re-evaluation of the chromosomes in light of the specific sacral malformation following the mapping of the Currarino syndrome gene to the tip of chromosome 7q showed that she had a terminal deletion of this region of the chromosome. Analysis of parental chromosomes showed that the unbalanced chromosome arrangement in the patient arose from a balanced translocation in the mother, in whom the terminal region of chromosome 7q was translocated onto chromosome 8q.

#### Case 2

A male infant (patient III:1, Fig. 2) born at 30 weeks gestation by normal vaginal delivery, following spontaneous rupture of the membranes presented on the 3rd day of life with abdominal distension and bile-stained vomiting. An abdominal radiograph showed dilated loops of intestine down to a narrow rectum. Rectal examination revealed a stenosis which was dilated from Hagaw size 3 to 10. Repeated dilatations were continued over the first weeks of life and regular bowel function was established.

Sacral dysgenesis was diagnosed on the plain abdominal radiograph, which showed marked dysplasia of the sacrum with only

---

**Fig. 1** Radiograph of the lumbosacral spine in case 1 aged 5 years showing malformation of the sacrum. The dysplastic sacrum is formed of two segments only

**Fig. 2** The family tree of case 2

---