

Review article

Autosomal dominant sacral agenesis: Currarino syndrome

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Abstract

Autosomal dominant sacral agenesis is characterised by a partial agenesis of the sacrum typically involving sacral vertebrae S2–S5 only. Associated features include anorectal malformation, a presacral mass, and urogenital malformation. Together, these features have been defined as the Currarino syndrome. Recently, *HLXB9* has been identified as the major causative gene in Currarino syndrome allowing identification of asymptomatic heterozygotes. In this review, we have performed an analysis of medical publications, and our own additional cases, to identify the range of malformations and complications that occur. We have also estimated risks of malformation in heterozygotes by using Weinburg's proband method on families personally known to us in order to provide accurate genetic counselling information.

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Sacral agenesis is defined as the congenital absence of the whole or part of the sacrum. It has a heterogeneous aetiology. In its classical form, often described as the caudal regression syndrome, there are malformations of structures derived from the caudal region of the embryo, that is, the urogenital system, the hindgut, caudal spine and spinal cord, and the lower limbs. Approximately 15–25% of mothers of these children have insulin dependent diabetes mellitus.

An autosomal dominant form of sacral agenesis sometimes described as a partial sacral dysgenesis also exists, in which typically there is a hemisacrum with preservation of the first sacral vertebrae. There have been approximately 90 case reports describing this distinct type of sacral defect since the first report in 1838.¹ In its most severe form, the hemisacrum is associated with a presacral mass (anterior meningocele, enteric cyst and/or presacral teratoma) and anorectal stenosis. This association was first described by Currarino *et al*² in 1981 and named the Currarino triad. A familial tendency was noted in some early case reports^{3–9}

with autosomal dominant inheritance first being recognised by Yates *et al*¹⁰ in 1983 (MIM 176450). There is an abundance of names describing this type of sacral agenesis and little consensus as to the most appropriate term. Some authors have used the term Currarino triad, others have described the syndrome as ASP (anal atresia, sacral anomalies, presacral mass), others as hereditary sacral agenesis, and finally there have been occasional reports describing this condition as part of the “caudal regression spectrum”. Belloni *et al*¹¹ called the disorder Currarino syndrome. We propose that this is the most appropriate term to use to describe this distinct phenotype for two reasons: (1) Currarino was the first author to link many of the features seen and explain the association in embryological terms, and (2) there are often other features present than just the triad of hemisacrum, presacral mass, and anorectal malformation.

In 1995, the underlying gene defect causing Currarino syndrome was localised to chromosome 7q36 and, recently, mutations in a homeobox gene, *HLXB9*, have been identified in several affected patients.^{11–14} Mutations in the coding sequence of *HLXB9* have been identified in nearly all cases of familial Currarino syndrome and in approximately 30% of patients with sporadic Currarino syndrome.¹⁴ Mutations have not been identified in the remainder of sporadic cases which raises the possibility of an unidentified mutation elsewhere in the gene, somatic mosaicism, or genetic heterogeneity. Currarino syndrome exhibits variable expressivity and many heterozygotes are asymptomatic. Thus, the true incidence of the disorder is unknown. With the identification of *HLXB9* as a major causative gene in Currarino syndrome, we are now in a position to confirm diagnoses in asymptomatic heterozygotes and more accurately determine the true incidence of the disorder. Heij *et al*¹⁵ and Tunnell *et al*¹⁶ found a strong correlation with the presence of a sacral defect and both high and low rectal malformations. They estimated that between 45% and 59% of patients with high rectal malformations and 19% of patients with low rectal malformations were associated with agenesis of the sacrum. It is likely that a proportion of such cases will have Currarino syndrome and work to date

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Table 1 Clinical features present in 205 patients with Currarino syndrome

Feature	Percentage
Bowel obstruction in infancy	16
Chronic constipation in childhood	41
Perianal sepsis	11
Renal/urinary tract problems	35
Gynaecological malformation	19 females
Meningitis	11
Spinal cord tethering	14
Anterior meningocele	50
Presacral mass other (eg teratoma/lipoma/cyst)	42
Asymptomatic	33*

*Asymptomatic subjects often have visible sacral defects on *x* ray; 13/90 (14.4%) of the asymptomatic cohort in our own series had a visible sacral defect. In only two cases was a mutation detected in an asymptomatic subject with no signs on *x* ray.

suggests that many of these patients will have mutations in *HLXB9*.^{11 13 14}

The aim of this paper is to review the clinical findings in patients with Currarino syndrome and to provide accurate information for genetic counselling purposes.

We present clinical information compiled from review of reports and personal contact with 205 patients with Currarino syndrome. Cases were included if they or a family member had all three major features of the syndrome: hemisacrum, presacral mass, and anorectal malformation. For 193 patients, clinical information was collected from 58 published reports (of which two families had been personally assessed by SAL and additional information from a further six families was provided by the authors) and information is presented for the first time on a further 12 unrelated subjects and their family members.^{2-10 17-65} While 59/205 cases were described as sporadic in nature, parental *x* rays were performed in only one instance (personal communication). Therefore, the remaining 146 cases, described as familial, are probably an underestimate as some of the reported sporadic cases may in fact be familial. Our assessment of the clinical features indicated no phenotypic difference between the two groups (familial and sporadic, data not shown) although this possibly reflects publication bias as only those cases with all the major features of Currarino syndrome will have been reported.

Results and discussion

There were 130 female (64%) and 75 male (36%) patients. The age range at presentation varied from birth to 64 years. Patients presented with a wide spectrum of signs and symptoms. The female excess is explained by

the associated gynaecological and urinary tract problems seen in women.

The manner, frequency, and diversity of presentations and the types of malformations seen are described in tables 1 and 2. From table 1 it can be seen that a broad range of clinical symptoms are associated with the Currarino syndrome affecting all caudal abdominal organs. Indeed, as can be seen from table 1, renal/urinary tract problems are almost as common as the three key features initially described.² Table 1 also shows the high proportion of patients in this study who are asymptomatic (33%), highlighting the variability in expressivity of the disease and illustrating the problem of defining accurately the incidence of Currarino syndrome.

Radiology (figs 1, 2, 3, and 4)

Classically, an anterior sacral defect is seen. The first sacral vertebrae is preserved although it may show subtle abnormalities. The defect usually takes the form of a sickle shaped or crescent shaped deformity of the sacrum, the hemisacrum or so-called scimitar sign (75% in our series). A bifid sacrum with a central defect was present in 22% and <5% had other more subtle abnormalities, including a pepperpot sacrum and coccygeal defects only. CT or MRI scanning is a useful tool particularly when planning resection of a presacral mass. Nowadays, with greater availability of MRI, it is considered a better alternative to CT scanning.²⁷

Surgical management

A thorough clinical examination including rectal examination may pick up both a sacral defect and a presacral mass in suspected cases. Examination by pelvic *x* ray is the initial investigation of choice. When present, bowel obstruction may be the result of (1) primary anorectal malformation, (2) secondary to obstruction from a presacral mass, or (3) spinal



Figure 1 Pelvic *x* ray of adult female showing a scimitar sacrum with a right sided defect. In our cohort, 38% had a sickle shaped sacrum with a left sided defect and 37% had a similar sickle shaped sacrum with a right sided defect.

Table 2 Malformations/malfunction of different organ systems observed in Currarino syndrome

Organ system	Observed malformations/malfunction
Gastrointestinal tract	Anorectal malformation including imperforate anus, anorectal sinus, constipation, perianal sepsis
Urinary tract*	Duplex ureter, horseshoe or duplex kidney, neurogenic bladder, vesicoureteric reflux, recurrent urinary tract infections, urinary incontinence, secondary hydronephrosis
Gynaecological tract	Bicornuate uterus, rectovaginal fistula, septate vagina
Spinal cord	Spinal cord tethering, neuroenteric cysts
Other	<i>E coli</i> meningitis

*Investigation of the renal tract in accordance with the BPA standing committee on paediatric practice guidelines is recommended.⁷⁶



Figure 2 Pelvic x ray of male child showing a left sided sacral defect with associated faecal loading.



Figure 3 CT scan of pelvis showing a large anterior meningocele filling with contrast (this is the same patient as shown in fig 1).

cord tethering. In practice it is usually the result of a combination of two or more of these features. Surgical intervention in the neonatal period is required in those with severe anorectal malformation. Those with milder symptoms can be managed conservatively although a number will require colostomy surgery for intractable constipation and associated soiling. Relief of symptoms of constipation following removal of the mass or release of the cord is experienced by some but not all. The presence of perianal sepsis is an important sign as it may be indicative of an underlying presacral mass.¹⁸

Surgical resection of a presacral mass, whatever its nature, is advisable. Anterior sacral meningoceles and presacral teratomas may be occult or may be accompanied by local pressure symptoms (constipation, erosion into the rectum with subsequent meningitis, urinary incontinence, and female genital problems such as protracted labour, dysmenorrhoea, and dyspareunia), local neurological symptoms (sacral anaesthesia, lower extremity paraesthesias, disturbance of anal sphincter control), or central neurological symptoms (nausea and headache precipitated by straining or coughing). Rupture of a meningocele has been recorded.

Advice on the optimal surgical management is not the remit of this paper. However, a retroperitoneal approach (using the Kraske parasacral technique or a sacral laminectomy) is favoured when an anterior meningocele is present. Where a presacral teratoma is identified, in the absence of an anterior meningocele, a transabdominal approach is recommended. For further information on recommended surgical techniques, the authors advise reading specialised papers.^{18 28 67}

There have been two confirmed published cases of malignant change to a teratoma,^{10 21} one in a 53 year old man who died of other causes and the other in a 32 year old female who died as a result of the teratoma. However, there are other cases suggestive of malignancy: O'Riordain *et al*¹⁸ reported a girl who died from a brain tumour following recurrence of a presacral teratoma at the age of 4 years. Necropsy was not performed preventing confirmation of a possible metastatic spread. Interestingly, a further case of Yates *et al*¹⁰ died from a brain tumour aged 14 years, but again no histology was available. Norum *et al*²⁴ described a leiomyosarcoma in the presacral region in a woman with constipation whose granddaughter had the Currarino syndrome. This woman had no evidence of sacral agenesis on x ray, nor did her intervening daughter. Norum *et al*²⁴ speculated that this tumour was related to the syndrome. Therefore, while malignant change can occur, the risk is lower (approximately 1%) than the risk of malignant change in sacrococcygeal teratomas.

The clinical features of spinal cord tethering, which are easily missed, require surgical intervention to prevent the progressive nature of the problem and hence to reduce the significant morbidity that can occur.⁶⁸ The neurological dysfunction associated with tethered cord is related to decreased blood flow at the level of maximum traction (S2-S4) and it is this which results in sphincter dysfunction including symptoms of constipation, bladder dysfunction, and, in some cases, secondary hydrocephalus. Release of the tethering may improve symptoms although retethering may occur necessitating appropriate follow up.³⁶

Prenatal diagnosis

Prenatal ultrasonography may identify the presence of a presacral mass, although it is not an accurate investigation for someone at 50% risk. There is only one published case where a

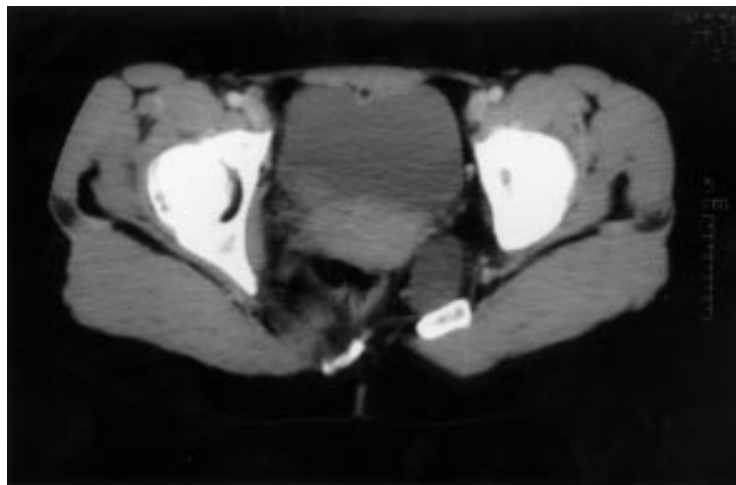


Figure 4 CT of pelvis of adult female showing gross distortion of pelvic anatomy with an abnormal sacral bone and a presacral mass.

prenatal diagnosis was made.²² In this case, the sacrococcygeal mass was unusually large for this condition. Prenatal diagnosis by mutational or linkage analysis is possible providing the mutation is known or the family structure is suitable.

Screening

All first degree relatives should be offered a pelvic x ray. The nature of the condition may result in large amounts of faeces obscuring the pelvic area making diagnosis difficult (fig 3). Since we identified the *HLXB9* gene as a major causative gene, we have found two subjects who carry family specific mutations but who have normal sacral x rays.¹³ However, most asymptomatic heterozygotes do have some abnormalities on x ray and this is still the investigation of choice. Relatives with an abnormal x ray should be referred to a surgeon for further investigations, including pelvic MRI or CT scanning for an occult presacral mass.

Genetic counselling

We have calculated accurate risk figures for counselling family members with this disorder by using Weinburg's proband method and including only those families known to our department. Information was available on 90 out of 110 first degree relatives from 13 families. All relatives of proven cases had a pelvic x ray. Of these, 44 (49%) were unaffected, 18 (20%) were clinically severe, 13 (14.4%) were clinically apparent with mild symptoms, 13 (14.4%) were asymptomatic but detected radiologically, and two (2.2%), who carry the family mutation, were asymptomatic with normal x rays. Of the 18 cases that were severely affected, 16 required bowel surgery, one had refused colostomy for intractable constipation, and one female patient had developed renal failure subsequent to a neurogenic bladder. This analysis indicates an autosomal dominant disorder with variable expression, reduced penetrance, and a low level of new mutation. Of the heterozygotes, 39% have a severe phenotype, 28.3% are clinically apparent, 28.3% have x ray changes only, and 4.4% are non-penetrant.

Cytogenetics

A number of case reports have described sacral agenesis and presacral masses in association with deletions of 7q.⁶⁹⁻⁷² We identified two sub-microscopic deletions in typical Currarino triad families and one deletion in an atypical family. All three families had the added feature of developmental delay. All had a normal routine karyotype; only one of the three deletions would have been identified using a commercially available FISH probe.

Molecular genetics

We have identified causative mutations in the coding sequence of the homeobox gene, *HLXB9*, in Currarino syndrome patients.^{13 14} This has been confirmed by other studies¹¹ and it is now clear that this gene is a major locus for Currarino syndrome.

To date, we have found a variety of different kinds of mutation: nonsense, missense, splice site, and frameshift. Mutations 5' of the homeobox are either nonsense mutations or frameshift mutations which introduce a stop codon before the homeobox, all the missense mutations are in the homeobox, and none of the mutations are 3' of the homeobox.¹⁴ In the majority of cases, a nonsense mutation is introduced either directly or as the result of a frameshift. Thus, it is likely that they represent loss of function alleles. This suggestion is supported by the similar phenotypes seen in patients with 7q36 deletions.⁶⁹⁻⁷² We identified mutations (using SSCP analysis covering all three exons) in *HLXB9* in 22/28 cases (78%) referred with features typical of Currarino syndrome. Mutations were detected in almost all familial cases (20/21) and in a proportion of sporadic cases (2/7), suggesting that *HLXB9* is the locus for familial Currarino syndrome. In sporadic cases, the failure to identify mutations in the majority of cases may be explained by mutations occurring outside the coding regions, the possibility of somatic mosaicism, or indeed genetic heterogeneity. There have been case reports of patients with cytogenetic abnormalities suggesting other locations for genes involved in the Currarino syndrome, for example 13q or 20p.⁷³ From our mutation detection data, we cannot exclude this possibility although it appears to be highly unlikely for familial cases. There were no obvious genotype/phenotype correlations other than that of developmental delay in those with large scale deletions involving *HLXB9* and probably other adjacent gene(s). In particular, there was no phenotypic difference between those with missense and those with nonsense mutations.

Of the total number of individual cases where a mutation was identified (22 in all), new dominant mutations were confirmed on molecular analysis in three (14%) subjects. It should be noted, of course, that our study arose from a linkage analysis study; these tend to focus on familial cases and the level of new mutation might be higher than this study suggests. We therefore cannot exclude a significant level of new mutation, but the published figures quoted of up to 50% would appear to be

exaggerated. Our study showed no cases of gonadal mosaicism.

The function of the *HLXB9* gene is unknown, although the presence of a homeobox makes it likely to be a transcription factor. If so, it will be of great interest to identify its target genes and partner protein(s) as a means of elucidating its role(s) in normal development. This should provide a basis for understanding its involvement in Currarino syndrome.

Differential diagnosis

Isolated sacral agenesis can occur as a consequence of diabetic embryopathy or because of unknown causes where it is described as the caudal regression or caudal dysplasia syndrome. The sacral defect tends to be more extensive, involving the first sacral vertebrae (S1) and often the lumbar and thoracic vertebrae.^{74 75} Sacral agenesis can also occur as an integral part of a number of syndromes including the VATER and OEIS syndromes, cloacal membrane malformations, and the Potter and X linked laterality sequence.⁷⁴ Each of these conditions is associated with specific malformations and differentiating between these diagnoses should not be a problem.

Sacroccoccygeal teratomas on their own are a distinct entity and most often present in the postcoccygeal region. They are three times more common in females and are present in antenatal life or at birth. The teratoma may be very large and necessitate caesarean section delivery. The underlying sacral bone is often normal. There is a high rate of malignant change with a greater tendency to malignant change in males.

Summary

Currarino syndrome is a rare autosomal dominant disorder and the human homeobox gene, *HLXB9*, is the major causative locus. Affected subjects are at risk of serious complications leading to significant morbidity and mortality. All families should be offered genetic counselling, as awareness of the disorder's hereditary nature ensures that first degree relatives are offered screening which allows identification of asymptomatic heterozygotes. Prompt diagnosis and surgery can help minimise the morbidity and recognition of at risk subjects should lead to better planning of pregnancies and appropriate management of affected children at birth.

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