A possible human homologue for the mouse mutant disorganisation

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SUMMARY The mouse mutant disorganisation (Ds) is a semidominant gene with variable penetrance in heterozygotes and lethality in homozygotes; 67% of heterozygotes have multiple defects and the rest have single defects. Fifty-three percent have cranioschisis and exencephaly, 40% have hamartomas represented by papillae of variable size and shape protruding from the body, sometimes containing cartilage, and 33% have limb abnormalities.

A child is presented with defects similar to those seen in mice heterozygous for Ds. He had shortening of the upper and lower segments of the right leg with a popliteal web and nine toes on the same side. A finger-like structure arose from the abdomen and one kidney was absent.

The homology between this infant and Ds mice is discussed and published reports of human cases with similar abnormalities are reviewed.

The mouse mutant disorganisation (Ds) was first fully described by Hummel,1,2 who stated that it received its name "from the fact that it disrupts the orderly processes of organogenesis and induces a great variety of developmental anomalies in structures derived from germ layers". The mutant is autosomal dominant with lethality in homozygotes and incomplete penetrance in heterozygotes. In affected heterozygotes, approximately two-thirds of animals have multiple defects and one-third single defects. The range of abnormalities caused by the mutation is shown in table 1. These can be roughly grouped into craniofacial abnormalities (cranioschisis/exencephaly, facial clefting, eye defects, pharyngeal defects), limb abnormalities (duplication and reduction, polydactyly, malformation of limb girdles), urogenital abnormalities (exstrophy/duplication of bladder, fused, cystic, or absent kidneys, malpositioned, atretic genital tracts), gastrochisis, and hamartomas. The hamartomas are an extremely interesting manifestation of the gene. They project from body surfaces and can resemble limbs, digits, urogenital papillae, mammae, or undifferentiated evaginations of skin. The hamartomas can also manifest as nodules in body walls and cavities and are made up of mixtures of tissues and

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Disorganisation (Ds): summary of abnormalities found in mice (from Hummel†).</th>
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</thead>
<tbody>
<tr>
<td>53% Cranioschisis/exencephaly</td>
<td>Complete absence of cranial vault Small defects of skull with encephaloceles</td>
</tr>
<tr>
<td>40% Hamartomas</td>
<td>Projecting from body surfaces and resembling limbs, digits, urogenital papillae, mammae, or undifferentiated evaginations of skin Nodules in body walls and cavities made up of mixtures of tissues and organoids (respiratory, digestive, urinary, and genital tracts)</td>
</tr>
<tr>
<td>33% Limb defects</td>
<td>Duplications and reductions, usually involving a single limb Polydactyly involving any ray, sometimes of high degree and undifferentiated Duplicated paw(extra limbs Malformed and small limb girdles</td>
</tr>
<tr>
<td>21% Eye defects</td>
<td>Open at birth Small, absent, or malpositioned Colobomata and folded retinae</td>
</tr>
<tr>
<td>18% Cranioopharyngeal defects</td>
<td>Hypoplastic mandible/maxilla Separation of nasal processes Facial clefts and cleft palate Pharyngeal pouch/fistulae Supernumerary hamartomatous tongues</td>
</tr>
<tr>
<td>16% Thoraco/gastrorchisis</td>
<td></td>
</tr>
<tr>
<td>&lt;15% Tail defects, rachischisis, urogenital and digestive tract anomalies</td>
<td>Curled, shortened, or missing tails Duplicated or atretic bowel Exstrophy/duplication of bladder Fused/cystic or absent kidneys Malpositioned/atretic genital tracts or gonads</td>
</tr>
</tbody>
</table>

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organoids (for example, respiratory, digestive, urinary, or genital tract).

With such a variable gene, causing often lethal malformations, it is difficult to identify human subjects who might have a homologous mutation. We present a child with features very similar to the manifestations of the mouse gene disorganisation and review similar published cases.

Case report

This is the second child born to a healthy, non-consanguineous 25 year old mother and a 30 year old father. An older brother is healthy. The pregnancy and birth were normal and the child's neonatal and early development have been within normal limits. On examination at four months there was a severe abnormality of the right leg, with shortening of the upper and lower segments and a web across the popliteal fossa, with flexion of the knee. The foot was inverted and had nine toes, none being identifiable as a hallux (fig 1). There was a large pad of tissue in the right groin and another over the right buttock with overlying flat vascular naevi. Just above the right anterior superior iliac spine a digit was attached to the abdominal wall. This digit contained bone and muscle and had a nail on the terminal 'phalanx' (fig 2). The left leg and both arms were entirely normal. Radiological investigations showed absence of the right kidney.

Discussion

The abnormalities caused by the mouse mutant gene disorganisation are many and various. They are summarised in table 1. Many of the abnormalities would be classified as multifactorial in origin, or sporadic, if seen in isolation in a human fetus or neonate. It is only if they appeared in unusual combinations in the same person that homology with the mouse mutant gene might be questioned. The case presented here has a very unusual combination of a high degree of polydactyly on one leg, a digit arising from the lower abdomen, and an absent kidney. It is difficult to explain these defects using classical embryological theory, and there is convincing similarity to the phenotypic effects of the mouse disorganisation gene.

FIG 1 Abdomen and lower limbs. Note inverted right foot with nine toes, digit-like structure arising from lower abdomen, and fat pad in right groin.

FIG 2 Close up of digit-like structure arising from abdomen; note nail.
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### TABLE 2  Summary of cases with duplicated lower limbs.

<table>
<thead>
<tr>
<th>Report</th>
<th>Limb defects</th>
<th>Other abnormalities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wells³ (Case: Blanche Dumas)</td>
<td>Extra leg and traces of a fourth</td>
<td>Dual independent external genitalia. Extra breast by the side of the fourth leg</td>
</tr>
<tr>
<td>Zammit⁴</td>
<td>Extra leg arising from pelvis posteriorly</td>
<td>Appendage containing bone below knee of extra limb. Clitoris and labium at base of extra limb. Mucous membrane covered tumour the size of an orange covered by 'labium'</td>
</tr>
<tr>
<td>Deboo⁵</td>
<td>Extra hypoplastic leg between normal pair</td>
<td>Two urethras. Abnormal ischial and pubic bones</td>
</tr>
<tr>
<td>Smillie and Murdoch⁶</td>
<td>Extra leg arising from right side of buttock.</td>
<td>Extra scrotum and penis with bifid glans. Glans and blind ending urethra arising from anteromedial aspect of extra leg</td>
</tr>
<tr>
<td>Norman⁷</td>
<td>Extra leg with three toes arising from left buttock</td>
<td>Cyst in 'buttock' of extra leg. Two digit-like fibroepithelial polyps arising from surface of the cyst</td>
</tr>
<tr>
<td>Srivastava and Garg⁸</td>
<td>Partial duplication of right foot. Eight toes in all. Double femora, single tibia, duplication of fibula</td>
<td></td>
</tr>
<tr>
<td>Cornah and Dangerfield⁹</td>
<td>Shortening of right leg. Duplicated femur, absent tibia</td>
<td></td>
</tr>
<tr>
<td>Taniguchi et al²⁰</td>
<td>Extra hypoplastic leg arising from left buttock. Five undifferentiated toes</td>
<td>Anal atresia. Rectovesicular fistula. Absent left kidney; hyperplasia of right kidney with vesicoureteric reflex</td>
</tr>
<tr>
<td>Billett and Bear¹¹</td>
<td>Duplicated right foot with seven toes</td>
<td>Absent right kidney. Postero-medial mass arising from right buttock, mainly adipose tissue</td>
</tr>
<tr>
<td>Hanley and Stanitski¹²</td>
<td>Duplicated left foot with six undifferentiated toes. Duplicated tibia</td>
<td></td>
</tr>
<tr>
<td>Stevenson et al¹³</td>
<td>Reduction of right leg with absent foot. Foot with four toes arising from perineum</td>
<td>Absent right kidney. &quot;Disrupted genital morphology&quot;. Hemi-vertebrae D8, D11, disorganised sacrocccygeal vertebrae. Spinal dermoid (7 with ectopic Wilms' tumour). Lipoma of cord</td>
</tr>
<tr>
<td>Schooley and Leichtman¹⁴</td>
<td>Atrophy of left leg. Third 'hypoplastic leg' arising from base of fluid filled sac over lower lumbar spine and sacrum</td>
<td>Duplicated external female genitalia with three labia majora and two vaginal openings. Left rectovaginal fistula. Very abnormal vertebrae below L1. Maternal trauma at three and 10 weeks' gestation</td>
</tr>
<tr>
<td>Present case</td>
<td>Shortened right leg with popliteal web. Right foot with nine undifferentiated toes</td>
<td>Finger-like structure arising from abdomen. Large pad of tissue over right inguinal region and over buttock. Absent right kidney</td>
</tr>
</tbody>
</table>

**"A 1 cm cutaneous protuberance without corporeal tissue or meatus at the usual position for the penis, a 1 cm slit-like urinary orifice located 1 cm posterior to this structure, palpable corporeal tissue embedded in the tissue to the left of this orifice, a left labioscrotal mound without a palpable gonad. Posterior to the labioscrotal mounds and the implanted foot was a slit-like anus."**
Review of published reports shows several case reports of persons with an extra lower or duplicated limb (table 2). In many of these cases there have been degrees of polydactyly associated with the extra limb, with additional features such as skin tags, lipomas or hamartomas, and genitourinary abnormalities.

For example, in the female reported by Wells there were dual independent external genitalia, two extra legs, and a breast like structure at the base of the fourth leg. In the case reported by Zammit there was an extra leg, which also had a small, fleshy appendage below the knee. There was a mucous membrane covered tumour the size of an orange at the base of the extra limb, which was interpreted as a clitoris and labium. More recently, the case reported by Schooley and Leichtman had a cyst over the lower spine, an extra hypoplastic leg arising from the base of this cyst, and duplicated external female genitalia. There were also multiple vertebral defects.

Several cases have had unilateral absent kidneys, for example, those of Taniguchi et al., Billett and Bear, Stevenson et al., Weisselberg et al., and the case presented here.

Families where there is clustering of different congenital abnormalities in several generations might point to the existence of a disorganisation-like gene. For example, Hoon and Hall have recently described a family in which a mother had both preaxial polydactyly and limb deficiency while the son had only limb deficiency. The maternal great grandmother was reported to have had a short left leg and a maternal first cousin on the mother's father's side had shortening of both fingers.

In view of the wide variety of abnormalities caused by the mouse disorganisation gene, it is obviously easy to overdiagnose possibly homologous human patients, who may have just one or two suggestive abnormalities. Features that should raise suspicion of a possible disorganisation-like gene are extra limbs, appendages, or hamartomatous structures, in association with polydactyly or partial duplication/reduction of limbs and apparently embryologically distinct malformations, such as urogenital, body wall, and craniofacial abnormalities. Asymmetry of malformations is a further pointer.

We would like to thank Dr J G Hall for pointing out the family segregating for a possible disorganisation-like gene and for helpful discussions.

References

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