

**SYNDROME OF THE MONTH**

**Weyers' ulnar ray/oligodactyly syndrome and the association of midline malformations with ulnar ray defects**

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**Abstract**

We describe a two generation family with variable ulnar and radial ray reduction and midline craniofacial abnormalities. The features suggest a diagnosis of Weyers' ulnar ray/oligodactyly syndrome originally described in two isolated cases. Syndromes of ulnar ray reduction are briefly reviewed and the

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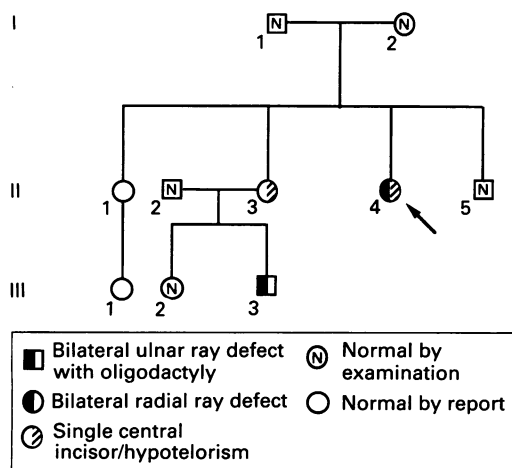


Figure 1 Family pedigree.

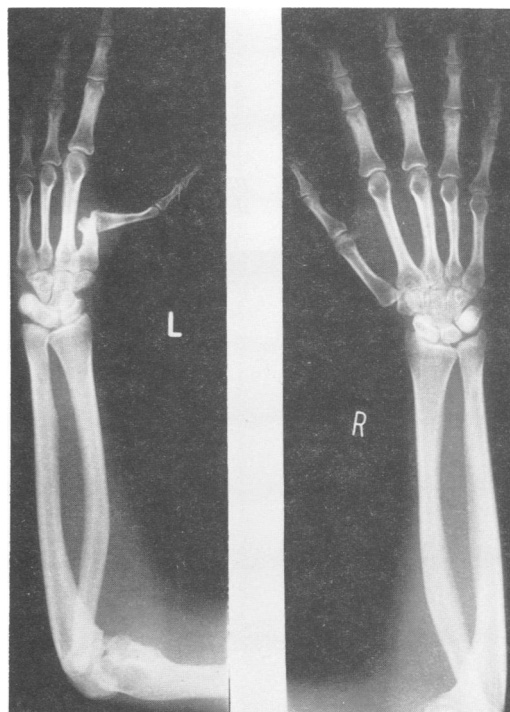


Figure 3 Radiograph of the forearms of II.4, aged 15½ years. The left index finger has been pollicised and there is bilateral dislocation of the proximal radial heads.

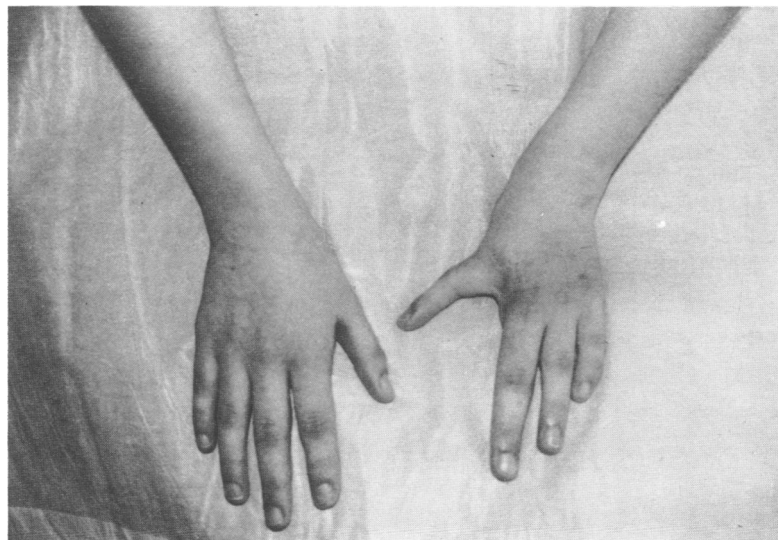


Figure 2 Appearance of the forearms of II.4, with mild bilateral preaxial defects, more severe on the left.

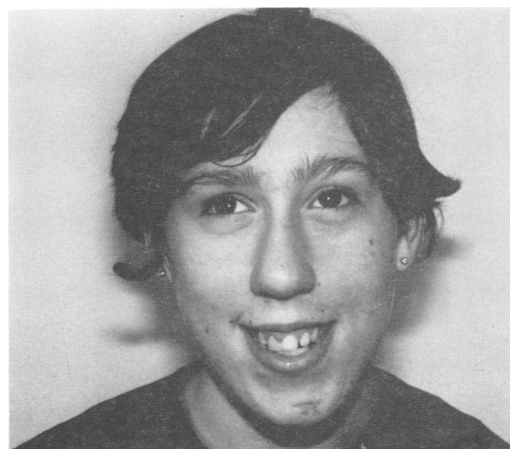


Figure 4 Facial appearance of II.4 showing a single central upper incisor after orthodontic surgery, aged 15½ years.



Figure 5 Appearance of III.3 as a newborn infant showing bilateral ulnar ray reduction.

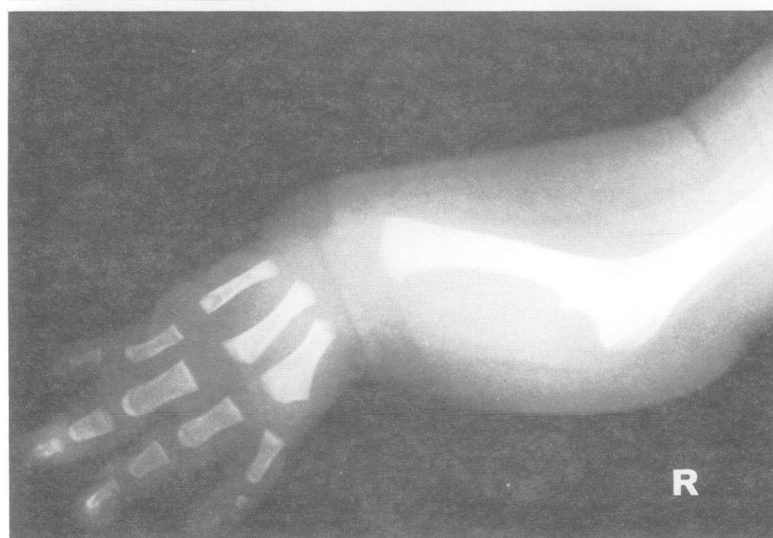
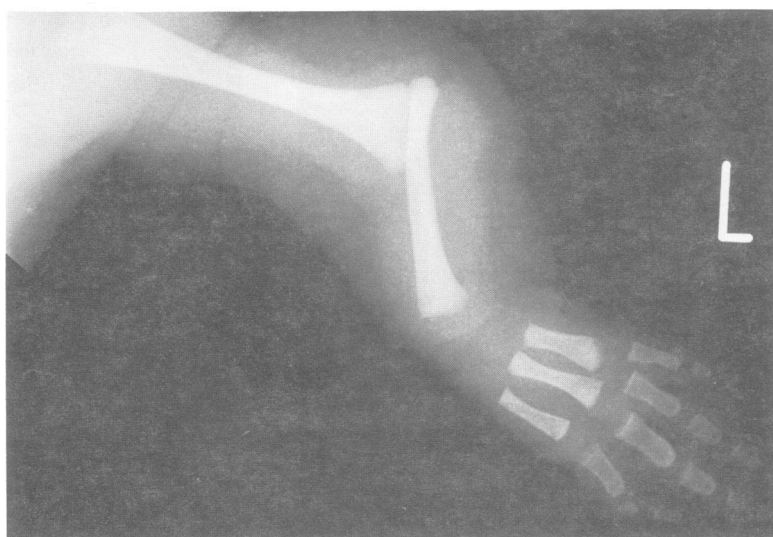


Figure 6 Radiographs of the forearms of III.3 showing oligodactyly, short radii, and (above) aplasia of the left ulna, (below) severe hypoplasia of the right ulna.

### relationship between limb bud and midline development discussed.

(*J Med Genet* 1992;29:659-62)

Reduction defects of the ulnar ray are very rare with a quoted incidence of 1:100 000.<sup>1</sup> They can occur as an isolated defect or as part of multiple congenital abnormality (MCA) syndromes. The relative frequency of isolated defects compared with the MCA group is not determined. MCA syndromes involving ulnar ray reduction appear diverse with few clearly recognisable patterns evident. In 1957 Weyers<sup>2</sup> described two unrelated children with ulnar ray deficiency, one with a single central maxillary incisor and hypoplastic mandible, the other with cleft lip and palate, fibular ray reduction, and renal and splenic abnormalities. In 1985 Elejalde *et al*<sup>3</sup> applied the Weyers' eponym to a lethal malformation in two sibs with ulnar and fibular ray deficiencies and hydronephrosis, proposing autosomal recessive inheritance. There are no other reports designated as Weyers' syndrome but midline abnormalities occur frequently within the ulnar ray/MCA syndrome group,<sup>4-15</sup> suggesting the possibility of a common developmental field of the ulnar ray and midline. These are presented in pedigree form following a description of our own two generation family, which has features favouring a diagnosis of Weyers' syndrome but with marked variability of expression.

### Family report

The proband (II.4, fig 1) was referred aged 14 years. On examination she had an absent left thumb with pollicisation of the index finger, mild mesomelia of the left forearm, bilateral dislocation of the proximal radial heads, and a proximally placed right thumb (figs 2 and 3). She had a long narrow face with hypotelorism, high arched palate, and a single central incisor (fig 4, aged 15½ years after orthodontic surgery). Head circumference and height were both on the 25th centile and a syndrome diagnosis was not reached at that time. There was

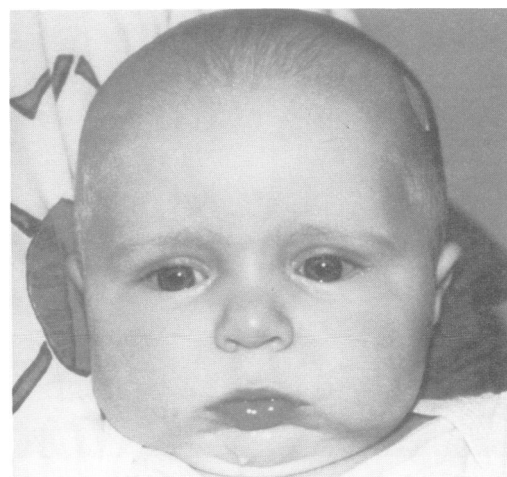


Figure 7 Normal face of III.3 aged 3 months.

good evidence she had suffered a congenital rubella infection, but apart from educational difficulties her features were not typical of this. Six months later her nephew, III.3, was born with bilateral oligodactyly and short radii, absent left ulna, and severe hypoplasia of the right ulna bone (figs 5 and 6). He had no apparent midline facial anomaly (fig 7) and at 9 months his dentition was normal. His mother,

II.3, had mild hypotelorism but was otherwise normal, as were the other members of the pedigree. Standard karyotyping and chromosome fragility studies for II.4 and III.3 were normal. Renal ultrasound was performed on III.3 only and was normal.

**Discussion**

Isolated ulnar ray defects appear to be reported less frequently than ulnar ray/MCA syndromes. These syndromes are dominated by the association of various midline developmental abnormalities, a review of which is presented in pedigree form in fig 8, with craniofacial abnormalities,<sup>4-9</sup> with congenital heart disease,<sup>10-12</sup> and with urogenital anomalies.<sup>13-15</sup>

Our family (fig 1) appears to be the first reported with a designation of Weyers' syndrome in which more than one generation shows manifestations, though the family reported by Steinfeld<sup>5</sup> is similar. There is marked variability between affected subjects, from severe bilateral postaxial limb reduction in III.3 to mild bilateral preaxial reduction in II.4. Subject II.3 shows non-penetrance for limb defect. The craniofacial midline defect varies from a single maxillary central incisor in II.4 to mild hypotelorism in II.3, with III.3 apparently normal. Weyers' own cases showed considerable variation but a midline facial defect was common to them. Unlike Weyers' cases there is no evidence for renal or other visceral anomalies in our family.

**Differential diagnosis**

Recognisable syndromes with ulnar ray reduction are few (for example, the ulnar-mammary syndrome)<sup>14</sup> but commonly involve midline structures and reports show both diversity and variability (fig 8). Other forms of limb reduction are also often associated with midline defects, for example, Holt-Oram and oroman-dibular-limb hypogenesis syndromes.

**Aetiology and genetic aspects**

The association of midline developmental anomalies with ulnar ray reduction, radial ray reduction, and phocomelic syndromes, suggests an intimate but as yet undefined embryological relationship between the limb buds and the midline. The processes which determine symmetry in the midline plane of the early embryo may therefore interact, or have a common developmental link, with the way in which mesenchymal condensations arise from the mesoderm to form the limb buds. Evidence in favour of a relationship between the midline and limb buds includes the variety of syndromes with similar phenotypes whose inheritance ranges through sporadic,<sup>12,15</sup> dominant with variable expression and penetrance,<sup>5</sup> to recessive and lethal.<sup>10</sup>

Apart from our own family there is at least one other two generation family reported where the limb reduction defect varied between preaxial and postaxial.<sup>8</sup> One review of

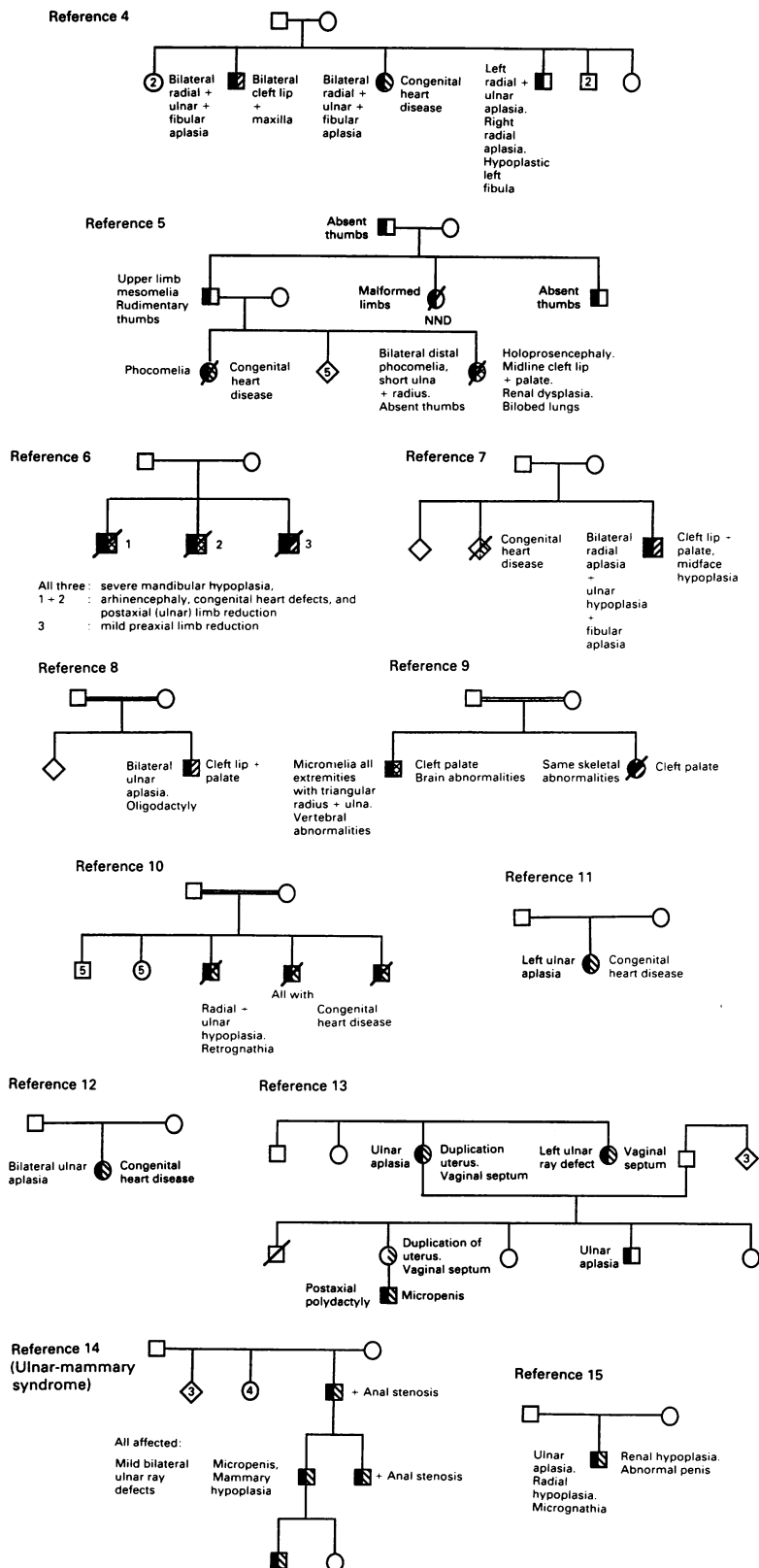


Figure 8 Pedigrees of published families.

39 cases of Holt-Oram syndrome included 15 with abnormalities or defects of the ulna<sup>16</sup> but intrafamilial variation was not commented on. The classification of limb reduction syndromes according to preaxial and postaxial defects may therefore not be appropriate, given that in some families different subjects, presumably with the same genotype, can have manifestations in either region. It appears that the result of gene damage affecting the development of the midline and limb buds together is not necessarily specific in the limb bud, but seems to vary, perhaps depending on local physiological gradients and intercellular communication. Recent studies in chick and mouse embryos show a correlation between homeobox gene expression and the bifurcation of forearm bones,<sup>17</sup> suggesting that these genes may be involved in the interpretation of positional signalling in limb differentiation. It may be that the same gene damage which causes dysmorphogenesis of midline body structures may also result in loss of specificity in radioulnar differentiation owing to disturbance in signalling of orientation around the limb bud longitudinal axis.

Proof of this hypothesis depends on the demonstration of gene transcripts showing expression both in midline structures and in the limb bud.

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