7-1-2009

# Classification and developmental biology of congenital anomalies of the hand and upper extremity

Paul R. Manske
*Washington University School of Medicine in St. Louis*

Kerby C. Oberg
*Loma Linda University*

# Classification and Developmental Biology of Congenital Anomalies of the Hand and Upper Extremity

By Paul R. Manske, MD, and Kerby C. Oberg, MD, PhD

Congenital anomalies of the hand and upper extremity are classified according to appearance; thus, the myriad of disparate presentations are organized into groups that share common morphologic features. The primary purpose of a classification is to enhance communication about the specific features of a condition by providing a descriptive framework for clinicians. Therefore, classification schemes should reflect the full spectrum of morphologic abnormalities within a given condition, and should be uncomplicated and easy for clinicians to remember and use. While an ideal classification would also guide treatment, provide insight into prognosis, and incorporate the etiologic mechanism of the condition, congenital classification systems often fall short of these goals.

The embryological development of the upper limb proceeds along three axes: proximal-distal, anterior-posterior (referred to postnatally as radial-ulnar by clinicians, because the fetal upper limb rotates during development), and dorsal-ventral[1]. The apical ectodermal ridge and the underlying mesoderm control proximal-distal development through a reciprocal loop of fibroblast growth factors and Wnt proteins[2]. The zone of polarizing activity located in the posterior (ulnar) limb mesoderm expands and posteriorizes the limb along the anterior-posterior (radial-ulnar) axis through a secreted morphogen, sonic hedgehog (SHH)[3]. The apical ectodermal ridge and the zone of polarizing activity are closely linked by a reciprocal feedback loop that maintains SHH expression at the posterior (ulnar)-distal border of the apical ectodermal ridge during progressive outgrowth. Dorsal ectoderm controls limb dorsalization through the secretion of Wnt7a and the induction of Lmx1b in the underlying dorsal mesoderm[4]. A reciprocal feedback loop between Wnt7a and SHH has also been demonstrated[5]. Thus, the integration of SHH into the pathways that control proximal-distal, anterior-posterior, and dorsal-ventral axes ensures coordinated patterning during each phase of limb outgrowth and development (i.e., humerus, forearm, and hand).

Targeted disruption of these organizing tissues (apical ectodermal ridge, zone of polarizing activity, and dorsal ectoderm) or their associated molecular pathways has given us insight into the etiologies of congenital limb malformations. For example, transverse deficiencies can be created in animal models by removal of the apical ectodermal ridge[6] or disruption of fibroblast growth-factor signaling[7,8]; ulnar longitudinal deficiency can be produced by eliminating production of SHH from the zone of polarizing activity[9,10]; and double palms occur in the absence of Wnt7a or Lmx1b[4].

Although current classification schemes attempt to consider the morphologic features of the developing limb bud, they do not convey the molecular mechanisms disrupted in the production of these deformities. Consequently, current classification schemes have been criticized as being too simplistic. While it is possible that a more sophisticated molecular or genetic classification system could be devised, the complexities of nature's genetic "toolbox" that influence the development of multiple tissue and organ systems might result in a scheme too complex to be useful for practicing hand surgeons. Nevertheless, insights from developmental biology may help refine the morphologic classification scheme to more precisely represent underlying mechanisms and related developmental pathways.

## History

The history of the classification of congenital anomalies is rich, dating back to the mid-nineteenth century[11-13]. Saint-Hilaire initially classified these "vices of conformation" as slight or severe in 1829[14]. In 1831, Otto[15] grouped these "vices of organization" according to ten variations (number, size, form, position, connection, color, consistency, continuity, texture, and content). In 1832, Saint-Hilaire[16] focused on the variation in number and size of the limb-segment anomalies, coining the terms ectromelia, hemimelia, and phocomelia. Fort[17] added the categories of axial deviation and adhesion (i.e., syndactyly) in 1869. Leboucq[18] noted the longitudinal arrangement of defects, and Polaillon[19] applied the adjectives radial, central, and ulnar in 1884. Potel[20] distinguished between longitudinal and transverse anomalies in 1914. O'Rahilly ex-

**Disclosure:** The authors did not receive any outside funding or grants in support of their research for or preparation of this work. Neither they nor a member of their immediate families received payments or other benefits or a commitment or agreement to provide such benefits from a commercial entity.

panded the concept of intercalary deficiencies (i.e., phocomelia) in 1951[21,22].

Two important contributions from the German literature were made in the late nineteenth and early twentieth centuries. Kümmel in 1895[23] (subsequently modified by Nigst in 1927[24]) divided congenital anomalies into three categories: (1) defect malformation (i.e., deficiencies), (2) syndactyly (i.e., fusion of parts), and (3) polydactyly (i.e., excessive number of parts). Müller in 1937 noted that malformations could present as a continuum in varying degrees or in different stages of development[25]. This concept of "teratological progression" allowed anomalies to be graded according to morphologic severity; it also allowed grouping of anomalies that might have different morphologic appearances, thus simplifying classification schemes.

Several classification schemes evolved from these concepts, but none were universally adopted. They were not sufficiently inclusive of all congenital anomalies, and there were substantial terminologic differences, particularly between hand surgeons from the United States and Germany. The current classification scheme accepted by most hand surgeons was first proposed by Swanson in 1964[26,27] and was based on the premise that anomalies should be grouped according to parts of the limb that have been primarily affected during development. There were six basic categories in the initial proposal: failure of differentiation of parts, arrest of development, duplications, overgrowth, congenital circular constriction band syndrome, and generalized skeletal defects.

Following extensive deliberation by representatives of the American Society for Surgery of the Hand (ASSH), the International Federation of Societies for Surgery of the Hand (IFSSH), and the International Society for Prosthetics and Orthotics (ISPO), the classification groupings were reordered and expanded to include a seventh basic category (undergrowth). This classification was published in the orthotics and prosthetics literature in 1974[12], and as the first scientific article in the inaugural issue of the American volume of the Journal of Hand Surgery[28] in 1976. Termed the IFSSH classification, this includes the seven major categories as well as subcategories, subclassifications, and anatomic levels of anomalies and diagnoses (Table I).

Although this classification is comprehensive, it has been criticized by authors who have found it difficult to classify complex cases[29-33], particularly the complex spectrum of cleft hand and symbrachydactyly[34]. Knight and Kay presented a more detailed version in 2000[35], attempting to include all congenital anomalies while still maintaining the seven basic categories.

Recently, the Japanese Society for Surgery of the Hand[36] suggested a modification, adding two additional groups: abnormal induction of rays as group IV (thereby renumbering categories V through VIII), and unclassifiable cases as group IX. The proposed category of abnormal induction of rays attempts to incorporate the concept of causation as suggested by experimental studies[37,38]; the proposed category includes syndactyly (both simple and complex), the central polydactyly-cleft hand-osseous syndactyly complex, and triphalangeal thumb. These conditions would move from their current categories of failure of formation (transverse), failure of differentiation, and duplication on the premise that they represent induction abnormalities rather than formation abnormalities. This proposal has not been universally accepted; critics argue that the differences between abnormal induction and abnormal formation are primarily semantic rather than actual[39].

**TABLE I The Classification System Developed by the International Federation of Societies for Surgery of the Hand (IFSSH) in Partnership with Other Organizations[28]**

| |
|---|
| I. Failure of formation |
| II. Failure of differentiation |
| III. Duplication |
| IV. Overgrowth (gigantism) |
| V. Undergrowth (hypoplasia) |
| VI. Congenital constriction band syndrome |
| VII. Generalized skeletal abnormalities |

Tonkin recognized that problems arise when attempting to incorporate our current understanding of causation into a morphology-based classification, and further contended that grouping according to such categories as failed formation, failed differentiation, or duplication may be inappropriate[39]. He proposed focusing the classification purely on descriptive features, with the primary classification noting the location (i.e., arm, forearm, wrist, or hand) and subcategories listing the tissue involved (bone or soft tissue) as well as the specific morphologic features of the anomalies.

Nevertheless, the IFSSH classification, which has served as the basis for scientific discussion and communication for more than forty years, continues to be accepted by most hand surgeons. There are specific classifications for twenty diagnostic conditions within these seven categories, with eighteen of the twenty conditions included in the first three categories (seven conditions with regard to failure of formation; eight conditions with regard to failure of differentiation; and three conditions with regard to duplication). We will review each classification scheme within the IFSSH classification, integrating modifications made subsequent to the original descriptions and assessing the value of the schemes to clinicians. Finally, we will present new information regarding the underlying etiology of the various conditions and propose a modification to the IFSSH classification that is based on current concepts of developmental biology.

## Group I: Failure of Formation

Abnormalities regarding failure of formation have been subdivided into longitudinal and transverse deficiencies. The longitudinal deficiencies are grouped according to radial, central, and ulnar deficiencies, reflecting the location of the cellular abnormalities on the developing limb bud. Transverse deficiencies are grouped as terminal or intercalary (i.e., pho-

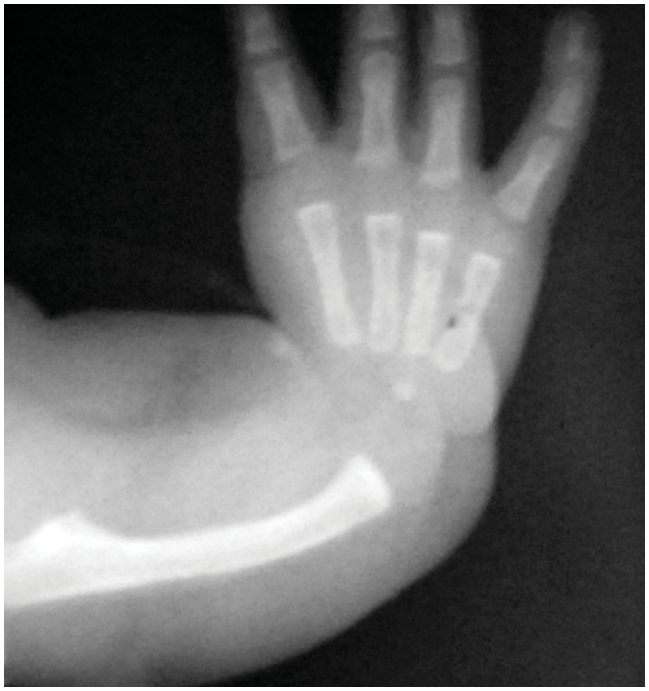

Fig. 1
Patient with type-IV radial deficiency and type-V thumb hypoplasia.

comelia) deficiencies. Recent studies have suggested that intercalary deficiencies are difficult to explain according to developmental biology concepts and may represent severe forms of longitudinal deficiency[40,41].

### *Radial Longitudinal Deficiency*

Radial longitudinal deficiency represents defects occurring at the preaxial (radial) border of the limb bud. Although skeletal and soft-tissue structures of the entire radial aspect of the upper extremity are progressively affected, the classification systems are based on (1) thumb hypoplasia, and (2) deficiencies of the radius (Fig. 1).

The underlying etiology of radial longitudinal deficiency is linked to decreased limb volume with intact SHH expression; thus, despite a reduction in tissue and frequently a reduction in overall limb length, posterior or ulnar elements are somewhat preserved. In animal models, progressive reductions in apical ectodermal ridge-associated fibroblast growth factors cause progressive reductions in the size of the developing limb bud and generate radial longitudinal deficiencies that closely correlate with what is seen clinically[42,43]. A number of molecular pathways impact cell growth or apoptosis, altering limb volume during the development of the forelimb or hand[9]. This susceptibility is reflected in the association of radial longitudinal deficiencies with a wide variety of syndromes and conditions[44].

#### Thumb Hypoplasia

Müller initially introduced four categories, expanded to five by Blauth in 1967[45]. Type I was subsequently defined more specifically by James et al.[46] in 1996, and type III was expanded by Manske et al.[47] in 1995.

*Type I.* Blauth[45] described this form of hypoplastic thumb as "minimal shortening and narrowing." James et al.[46] more clearly limited the deficiencies to aplasia or hypoplasia of the intrinsic muscles of opposition, that is, the abductor pollicis brevis and the opponens pollicis.

*Type II.* There are three specific features of type-II hypoplastic thumbs: (1) aplasia or hypoplasia of the intrinsic muscles innervated by the median nerve, sparing the ulnar-innervated intrinsic muscles; (2) narrowing of the thumb-index web space; and (3) instability of the metacarpophalangeal joint due to ulnar collateral ligament insufficiency.

*Type III.* The three manifestations of type-II hypoplasia are also present in type-III hypoplasia, frequently in more severe form. The narrowed thumb-index web space may present as a more distal takeoff of the thumb, and metacarpophalangeal joint instability may be global, also involving the radial collateral ligament.

There are two additional deficiencies in type-III hypoplasia[47]:

- Extrinsic muscle-tendon abnormalities, including absent extensor pollicis longus, absent or aberrant flexor pollicis longus, tendon interconnections between the extensor pollicis longus and flexor pollicis longus, and a variety of muscle-tendon interconnections at the volar aspect of the wrist and distal part of the forearm as described by Graham and Louis[48].
- Deficiencies at the base of the first metacarpal. In type III-A, the metacarpal base is hypoplastic but present and stable; in type III-B, the metacarpal base is absent and unstable.

*Type IV.* This form of hypoplasia is the classic *pouce flottant*. The thumb is attached to the hand by a skin bridge and neurovascular elements with no musculotendinous units or osseous structures stabilizing it to the hand.

*Type V.* The thumb is completely absent, although there may be rudimentary thenar muscles, tendons, or neurovascular structures along the radial border of the index metacarpal.

This classification system enhances communication, provides some prognostic information, and guides surgical decisions. Types I, II, and III-A deformities are treated with thumb reconstruction, while types III-B, IV, and V deformities are treated with thumb ablation and index-finger pollicization.

#### Deficiencies of the Radius

The predominant features of this classification include progressive skeletal deficiency of the radius along with radial angulation of the hand at the level of the wrist. Frequently referred to as "radial club hand," the condition is now more acceptably referred to as radial deficiency (or dysplasia).

The abnormal features can include general hypoplasia of the upper extremity, absent active elbow flexion or elbow flexion contracture, shortening and/or bowing of the ulna, and aplasia or hypoplasia of the scaphoid and other carpal bones. The thumb is always affected, and the fingers frequently have limited motion and function, progressing in severity from the

radial to the ulnar side of the hand. Radial neurovascular structures may be abnormal, and the radial musculotendinous structures may be absent or abnormal, often forming a firm fibrous band that tethers the wrist and hand, thus contributing to the radial angled position. The severity of these additional abnormal features parallels the severity of the radial deficiency.

Classification of the condition was initially presented by Bayne and Klug[49] as types I through IV in 1987, based on the radiographic appearance of the radius. The classification was expanded by James et al.[50] in 1999 to recognize radial-sided deficiencies limited to the carpus (type 0) and thumb (type N). More recently, the classification was extended by Goldfarb et al.[40] to include type V.

*Type N.* The radius and carpus are normal, with deficiencies limited to the thumb (see hypoplastic-thumb classification above).

*Type 0.* The radius is normal in length. The scaphoid and other radial carpal bones are hypoplastic or absent, thus potentiating radial angulation of the hand and carpus. Not all type-0 wrists demonstrate radial angulation; soft-tissue contraction of the radial joint capsule and musculotendinous structures are also necessary to produce the angulation. The thumb is hypoplastic.

*Type I.* Initially described by Bayne and Klug[49] as a "short distal radius," the description was more specifically defined by James et al.[50] as a distal portion of the radius that is >2 mm shorter than the distal portion of the ulna. The proximal portion of the radius is usually normal, but may be characterized by radioulnar synostosis or congenital dislocation of the radial head.

*Type II.* The radius is hypoplastic in its entirety, referred to by Bayne and Klug as "radius in miniature" with proximal and distal physes. This hypoplastic radius is often associated with severe bowing of the ulna.

*Type III.* The distal part of the radius (including physis) is absent.

*Type IV.* The radius is completely absent.

*Type V.* Proximal radial longitudinal deficiency was formerly considered a form of phocomelia. Frantz and O'Rahilly[21] initially proposed it as a severe intercalary segmental defect of the osseous structures of the arm and forearm. Recent authors[40,41] have challenged the concept of intercalary defects in that such defects are difficult to explain according to developmental biology concepts; rather, phocomelic upper limbs represent forms of longitudinal deficiency (radial, ulnar, or a combination of both)[40]. Extremities with type V radial longitudinal deficiency have the following characteristics:

- abnormal glenoid
- absent proximal portion of the humerus
- distal portion of the humerus articulates with ulna
- radial-sided hand abnormalities

This classification enhances communication but does not guide treatment decisions or provide prognostic information. It does attempt to incorporate concepts of abnormal developmental mechanisms.

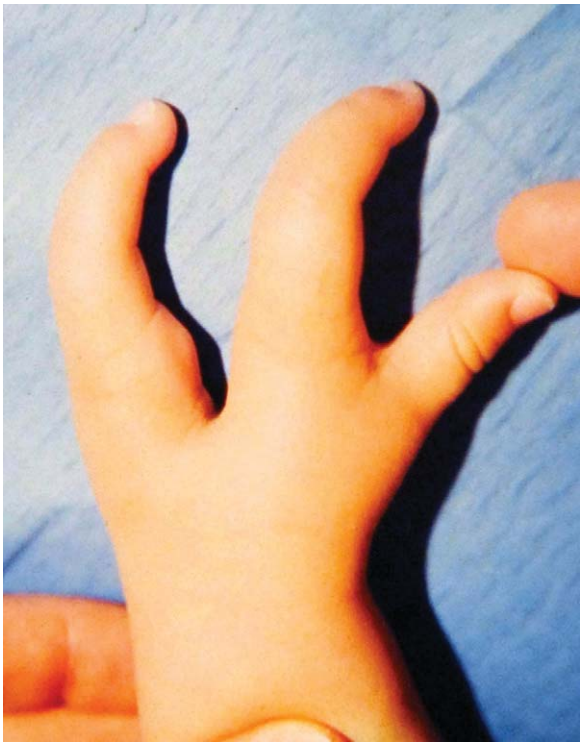

Fig. 2
The hand of a patient with a type-II (narrowed web) central deficiency.

### *Central Deficiency*

Central deficiency, also descriptively referred to as "cleft hand," represents suppressed development of bone and associated soft-tissue structures of the central part of the hand (or foot) (Fig. 2). The presentation can vary from a simple soft-tissue cleft between the long and ring fingers without loss of digits[51,52] to suppression of all osseous elements of the hand except for the little finger ray[53,54]. The defect does not include deficiencies of the wrist, but associated carpal coalition and proximal radioulnar synostosis have been reported[51]. Defects of the central or medial apical ectodermal ridge are responsible for central clefting[55]. Syndromic forms of this disorder exhibit mutations in genes that participate in apical ectodermal ridge function[55,56].

Central deficiency occurs in association with central polydactyly and syndactyly (soft-tissue and osseous)[53,54,57]. Ogino[58] produced this spectrum of defects in littermates of pregnant rats, thus suggesting an etiologic relationship between these conditions. In this animal model, there is diffuse cell death of the limb-bud ectoderm and mesoderm with reduced expression of multiple limb organizing factors, along with apoptotic factors and focal interruption of the apical ectodermal ridge[59]. These experimental observations are the basis for the proposed abnormal induction category[35] noted previously.

Various classification systems have been proposed that are based primarily on the characteristics of the central defect. Barsky[60] distinguished between typical cleft hand (deficiencies of the central rays with preservation of the marginal digits) and atypical cleft hand (central rays progressively reduced in size

with shortened marginal rays). However, current opinion is that the latter represents a form of transverse deficiency (symbrachydactyly)[57,61,62] and therefore is not appropriately included in the central deficiency classification. Several authors have classified the associated presence of central polydactyly and osseous syndactyly[53,63] as "atypical." Finally, several authors have classified the hand according to the number of deficient central osseous elements[51-54].

In hands with a central deficiency, the cleft is not functionally limiting but is aesthetically unsightly. Flatt[64] described the cleft as "a functional triumph and a social disaster." In addition to the central cleft, there is an associated narrowing of the thumb web space, which is a notable functional deficiency[65]. Consequently, surgical treatment of the cleft is primarily for aesthetic reasons, while surgical treatment of the narrowed thumb web is functionally important. The progressive narrowing of the thumb web space parallels the progressive deficiencies of the central cleft. Consequently, Manske and Halikis proposed a classification of the central deficiency that is based on the progressive narrowing of the thumb web space[65].

- Type I. Normal web. The thumb web space shows no narrowing.
- Type II. Narrowed web. The web space is narrowed, either mildly (type II-A) or severely (type II-B).
- Type III. Syndactylized web. The thumb and index rays are syndactylized, with complete obliteration of the web space.
- Type IV. Merged web. The osseous elements of the index ray are suppressed and the web space of the thumb is merged with the cleft, frequently in association with ulnar collateral ligament instability of the thumb metacarpophalangeal joint.
- Type V. Absent web. The thumb and radial digital elements are completely suppressed; only the ulnar ray(s) remain.

This classification system enhances communication and guides surgical reconstruction. In type I, the web space is normal and does not need reconstruction; therefore, cleft closure is the surgical focus. In types II-A, II-B, and III, the narrowed thumb web is surgically widened with use of local flaps or dorsal and/or volar transposition flaps from the cleft. In type IV, no reconstruction of the web space is necessary; reduction of an excessively wide web space and/or stabilization of the metacarpophalangeal joint may be necessary. In type V, first metacarpal lengthening or toe-to-hand transfer may be considered.

### *Ulnar Longitudinal Deficiency*

Ulnar longitudinal deficiency represents a spectrum of abnormalities that affect the ulnar border of the upper limb. Although the deficiencies follow the ulnar longitudinal axis in the forearm and upper arm, both the ulnar and radial sides of the hand can be affected (Fig. 3). Despite this apparent paradox, the abnormalities seen in ulnar longitudinal deficiency are best explained by disruption of the zone of polarizing activity that is present in the posterior (postaxial) region of the limb bud.

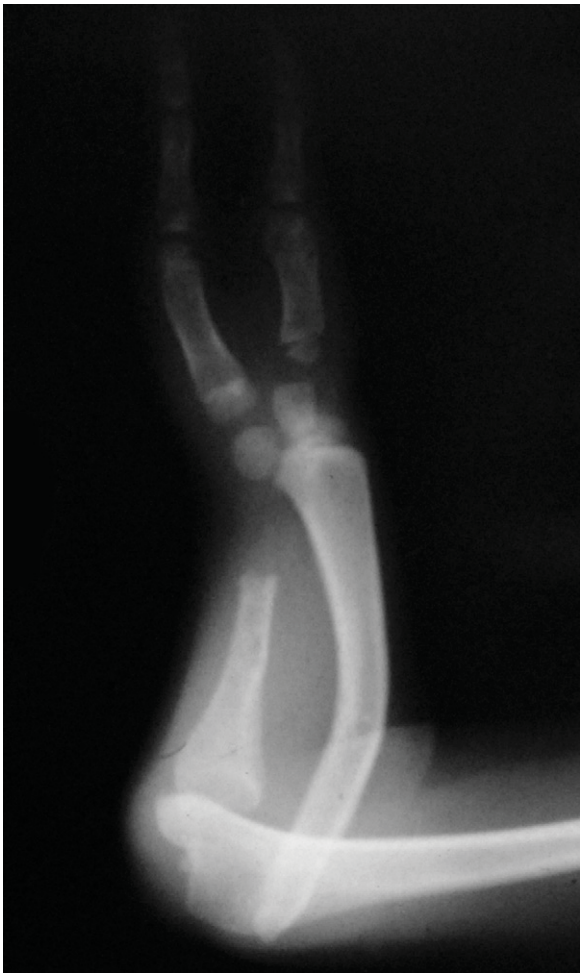

Fig. 3

Radiograph of a patient with a type-II ulnar longitudinal deficiency of the forearm and a type-C hand abnormality.

The zone of polarizing activity, via the secreted morphogen SHH, posteriorizes (ulnarizes) the developing limb. The spectrum of ulnar longitudinal deficiencies reflects variation in the timing, degree, and duration of SHH disruption. Furthermore, loss of SHH function also accounts for the radial involvement seen in ulnar longitudinal deficiency. Recent experiments in animal models demonstrate that, in addition to posteriorizing the developing limb, SHH also plays a role in limb proliferation, expanding the distal portion of the limb during development[9,10]. Thus, loss of SHH also reduces limb volume. Depending on the timing and extent of SHH disruption, the hand may also be involved. In mice, progressive digit loss with declining SHH function follows an unexpected pattern, with digit 3 being lost first, followed by digit 5, then digit 2, and finally digit 4[10]. This sequence of digit loss may help clarify carpal morphology and tendon attachments in the remaining digits in limbs with ulnar longitudinal deficiency.

Classification schemes for ulnar longitudinal deficiency are based on (1) forearm and elbow and (2) hand abnormalities.

**Forearm and Elbow**

Recent clinical reviews have reported only 222 cases of ulnar longitudinal deficiency[66]; nevertheless, six different classifications based on the deformities of the forearm and elbow have been presented[23,67-71]. While all of the categories are similar, the four-category classification of Bayne[67] is generally preferred. Of interest, none of the forearm-and-elbow classifications considers hand abnormalities; to address this limitation, Bayne's forearm and elbow classification has recently been modified[72] to include Type 0. Additionally, as noted in the presentation of radial deficiencies, Goldfarb et al.[40] have added Type V to include those phocomelic extremities with characteristics suggestive of ulnar longitudinal deficiency.

- Type 0. Normal-length ulna (i.e., distal aspect of the ulna at the level of the distal aspect of the radius) with ulnar-sided hand deficiencies
- Type I. Hypoplastic ulna with distal and proximal epiphyses present
- Type II. Distal ulnar aplasia
- Type III. Complete ulnar aplasia
- Type IV. Radial-humeral synostosis
- Type V. Proximal ulnar longitudinal deficiency[40]: hypoplastic glenoid; single arm and forearm bone that is usually bifurcated distally, with proximal features resembling a humerus and distal features characteristic of a radius; absent elbow joint; and hand abnormalities typical of ulnar longitudinal deficiency

While useful for facilitating communication, this classification does not guide treatment or provide prognostic information.

**Hand**

Several authors have noted the high prevalence (68% to 100%) of hand abnormalities (particularly abnormalities of the thumb) in ulnar longitudinal deficiency[38,73-77] as well as the fact that the majority of surgical procedures (55% to 75%) are performed for hand and thumb abnormalities[76] as compared with forearm abnormalities. Thus, the need for additional classification of hand abnormalities seems apparent. Ogino and Kato[38] classified hand abnormalities according to the number of missing rays, proceeding sequentially from the ulnar to the radial side of the hand, but did not include absence or abnormalities of the thumb.

In view of the high prevalence of thumb abnormalities and the importance of the thumb to the function of the hand, Cole and Manske proposed a system of classification based on features of the thumb[76], adding alphabetic letters to the roman numerals of the forearm and elbow classifications.

- Type A. Normal first web and thumb
- Type B. Mild first web and thumb deficiency
- Type C. Moderate to severe first web deficiencies: loss of opposition; malrotation of thumb into the plane of the fingers; thumb and index syndactyly; absent extrinsic tendon function
- Type D. Absent thumb

This classification enhances communication and provides information about the likelihood of surgical intervention, as surgical reconstruction is more commonly recommended for types C and D hands compared with types A and B hands.

*Transverse Deficiency*

Transverse deficiency includes both terminal and intercalary (phocomelic) deficiencies. There are two forms of terminal failure of formation: symbrachydactyly and transverse arrest (also known as congenital amputation). Although standard textbooks[78-85] have separate chapters for each form and the IFSSH classification places the two in separate categories (transverse arrest in failure of formation; symbrachydactyly in undergrowth), symbrachydactyly is probably a more distal manifestation of transverse deficiency, and transverse arrest (congenital amputation) is a more proximal manifestation[62,86-88]. This concept has received scientific support from Kallemeier et al.[89], who noted that 93% of extremities with transverse arrest at the level of the forearm had rudimentary manifestations of digits (finger nubbins, nail remnants, or skin invagination) which are seen in symbrachydactyly.

Summerbell[6] demonstrated a mechanism for transverse arrest by removing the apical ectodermal ridge from developing wing buds, correlating the timing of apical ectodermal ridge removal to level of truncation[90]. Fibroblast growth factors emanating from the apical ectodermal ridge promote mesodermal proliferation and impede apoptosis. Consequently, abating apical ectodermal ridge-associated fibroblast growth-factor signaling can also yield terminal truncations[7,8]. Recently, Winkel et al. demonstrated a link between Wnt signaling and ROR2, the receptor tyrosine kinase frequently mutated in brachydactyly type B (another name for symbrachydactyly)[91]. Wnt signaling is critical for apical ectodermal ridge-related fibroblast growth-factor expression and function; thus, this finding links abnormal apical ectodermal ridge function to symbrachydactyly and provides further evidence for inclusion as a transverse deficiency.

**Symbrachydactyly**

The four-category classification of symbrachydactyly (Fig. 4) was initially proposed by Pol[92] and subsequently adopted by Blauth and Gekeler[86] and others[87]

- Short finger type. This includes hands with short, underdeveloped, or absent middle phalanges.
- Oligodactylic type. Partial or complete absence of the central three fingers relative to the border (thumb and little finger) digits. This type was previously called "atypical" cleft hand (see above); it has also been referred to as the "cleft-hand type" of symbrachydactyly.
- Monodactylous type. Absence of all fingers, including parts of the metacarpals. The thumb is present but is of varying size and stature.
- Peromelic type. Absence of all digital rays with only digital nubbins and nail remnants.

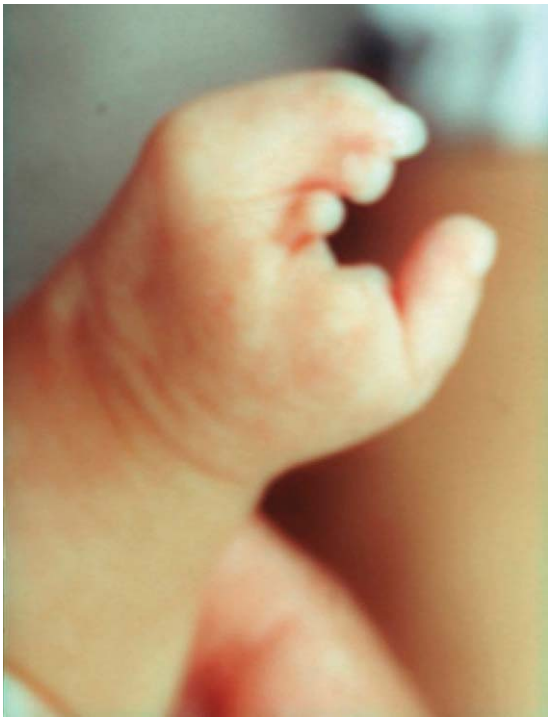

Fig. 4
Patient with oligodactyly-type symbrachydactyly.

**Transverse Arrest**

More proximal manifestations of transverse arrest (Fig. 5) are referred to as:

- Acarpia. Congenital absence at the level of the carpal bones.
- Congenital forearm amputation. Congenital absence at the forearm, also called congenital below-the-elbow deficiency.

These descriptive classifications enhance communication, but do not help with prognosis or treatment or incorporate concepts of underlying etiology.

*Intercalary Deficiency (Phocomelia)*

Intercalary deficiency has been considered a segmental transverse deficiency. It came into common usage in the early 1960s following the report by Frantz and O'Rahilly[21], who classified it according to three types:

- Type I. Complete phocomelia. Complete segmental deficiency of the arm and forearm, with the hand attached to the trunk.
- Type II. Proximal phocomelia. The humerus is absent, and the forearm and hand are attached directly to the trunk.
- Type III. Distal phocomelia. The forearm is absent; the hand is attached to the humerus.

On close inspection, these extremities usually do not demonstrate true segmental deficits; rather, the limb is abnormal proximal and distal to the segmental defect, challenging the existence of true intercalary deformities[28,40,41,93]. Furthermore, it is difficult to classify as much as 75% of extremities diagnosed as phocomelic with use of the features of the above classification. Instead, phocomelia most likely represents the most severe form of longitudinal deficiencies[40]:

- Proximal radial longitudinal deficiency. Characteristics as noted above (type V radial longitudinal deficiency).
- Proximal ulnar longitudinal deficiency. Characteristics as noted above (type V ulnar longitudinal deficiency).
- Severe combined dysplasia, type A. A normal or hypoplastic shoulder with an underdeveloped glenoid; a normal or short humerus with normal distal flare; absence of both radius and ulna; abnormal hand with features that do not correspond to either radial or ulnar deficiency.
- Severe combined dysplasia, type B. Complete absence of both the humerus and forearm segments; abnormal hand elements (unclassifiable according to radial or ulnar dysplasia deficiency) attached to an abnormal shoulder.

While the reclassification of phocomelia does not assist with determination of treatment or prognosis, it advances understanding of these conditions by incorporating current concepts of underlying etiology.

## Group II: Failure of Differentiation

Conditions categorized under failure of differentiation more aptly represent abnormalities of development rather than differentiation; yet, for the most part, they share a common theme in the disruption of hand plate (or foot plate) development and involve carpals, metacarpals, digits, or interdigital spaces. Several of these conditions have been classified.

*Syndactyly*

Syndactyly can be seen as an isolated condition or as a component of other conditions in the failure of formation and duplication categories. Programmed cell death or apoptosis between digits creates the interdigital space. This interdigital apoptosis is under the control of bone morphogenetic proteins (BMPs) and the associated regression of fibroblast growth-factor signaling in the overlying apical ectodermal ridge. In ducks and bats, where webbing is prominent between digits, there is inhibition of interdigital BMP signaling and persistent fibroblast growth factor[94,95]. Furthermore, targeted disruption in interdigital BMP signaling or abnormal fibroblast growth factor signaling leads to interdigital webbing or syndactyly[59,96].

Syndactyly is descriptively grouped according to the degree and complexity of the webbing[97,98], facilitating communication but with limited usefulness for determining treatment and prognosis (Fig. 6).

- Simple. Web contains only skin and soft tissues; the web extends either to the fingertip (complete) or to a point between the base and tip (incomplete).
- Complex. Web includes osseous interconnections between adjacent digits.

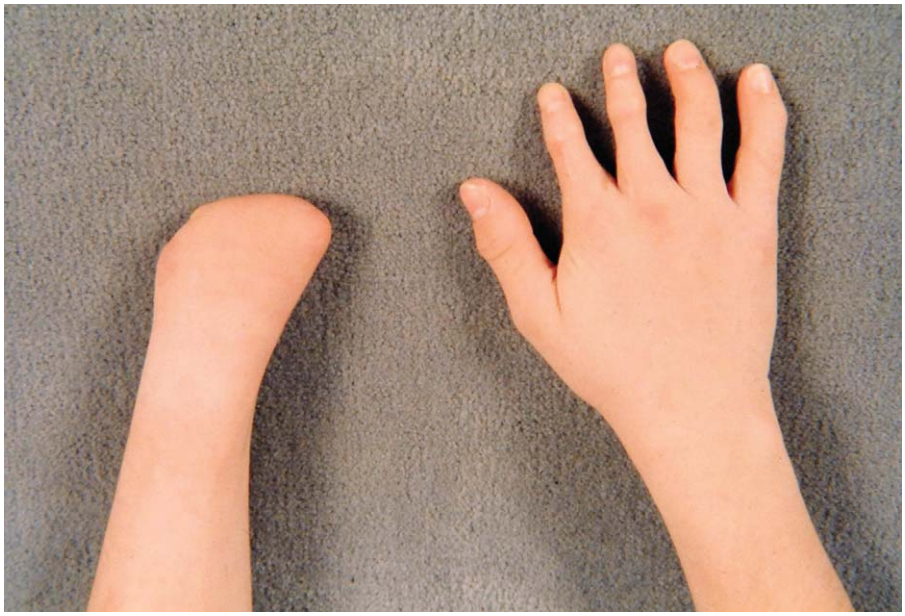

Fig. 5

Left hand of a patient with an acarpia form of transverse arrest.

- Complicated. Web includes osseous interconnections of more than two digits as well as neurovascular and musculotendinous interconnections.

*Apert Syndrome*

The acrosyndactyly seen in Apert syndrome is a severe deformity involving all five digits. There are two classification schemes. Upton's scheme considers the shape of the hand, specifically the involvement of the first web space and the configuration of the digital (finger) "mass."[99]

**Type I. Spade Hand**
- Incomplete syndactyly of first web
- Digital mass flat in palmar plane
- Good digital metacarpophalangeal joints
- Varying degrees of symphalangism

**Type II. Mitten (Spoon) Hand**
- Complete simple syndactyly of first web
- Digital mass forms palmar concavity
- Proximal metacarpals splayed
- Tight fusion of fingertips
- Synonychia of central nails

**Type III. Hoof (Rosebud) Hand**
- Complete complex syndactyly of first web
- Thumb incorporated into mass
- Hand tightly cupped
- Skeletal abnormalities of index ray
- Synonychia of central nails

While Upton's classification is purely descriptive, Van Heest et al. guides surgical planning in the staged reconstruction of the hand[100].

**Type I**
- No metacarpophalangeal angular deformity
- Parallel alignment of metacarpals and phalanges
- Surgical goal: four-fingered hand

**Type II-A**
- Mild angular joint deformity at metacarpophalangeal joints
- Extensive complex distal osseous syndactyly
- Surgical goal: three-fingered hand with third-ray resection

**Type II-B**
- Marked angular deformity at metacarpophalangeal joints (apex radial of second ray, apex ulnar of fourth and fifth rays)
- Extensive complex distal osseous syndactyly
- Second ray pronated, lies in plane of thumb
- Surgical goal: three-fingered hand with second-ray resection

**Type II-C**
- Marked angular deformity at metacarpophalangeal joints (apex radial of second and third rays, apex ulnar of fourth and fifth rays)
- Extensive complex distal osseous syndactyly
- Fourth ray supinated, lies in plane of digit 5
- Surgical goal: three-fingered hand with fourth-ray resection

*Camptodactyly*

Camptodactyly is a flexion contracture of the proximal interphalangeal joint, which can occur at birth or can present later

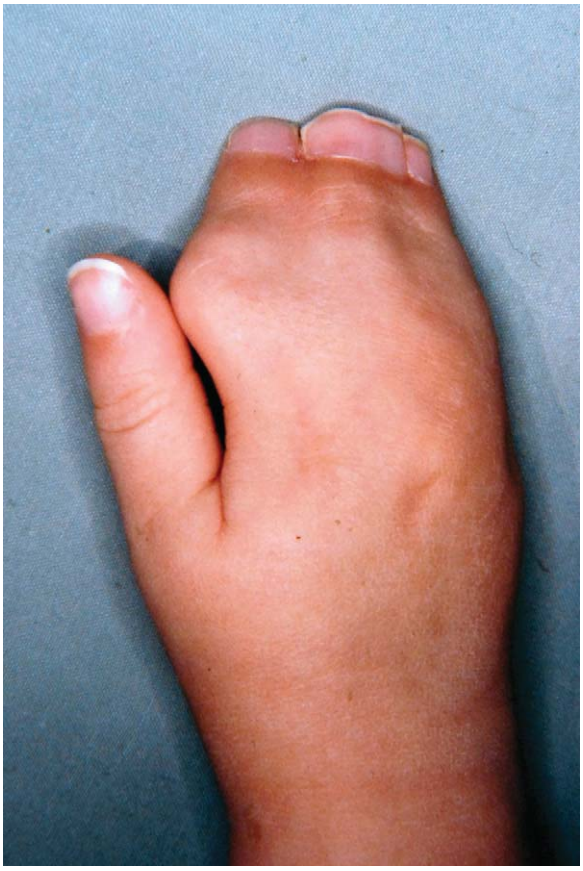

Fig. 6
Patient with complex syndactyly of the index, long, ring, and little fingers.

in childhood or adolescence (Fig. 7). The classification system of Benson et al. is based on the time of presentation and the associated conditions[101], providing useful descriptive and prognostic information.

- Type I. Occurs in infancy; usually an isolated finding limited to little finger; affects boys and girls equally.
- Type II. "Acquired," occurring at seven to eleven years of age; affects girls more than boys.
- Type III. Associated with a variety of syndromes; more severe, involving multiple digits; occurs bilaterally but asymmetrically.

*Clinodactyly*

Clinodactyly presents as radial angulation of the little finger due to triangular or trapezoidal shape of the middle phalanx. It usually occurs as an isolated condition, but on occasion can occur in association with syndactyly, polydactyly, or macrodactyly. Cooney's classification is purely descriptive[102].

- Simple. Osseous deformity, middle phalanx <45°
- Simple complicated. Osseous deformity, middle phalanx >45°
- Complex osseous deformity. Middle phalanx <45°; soft-tissue deformity (syndactyly)
- Complex complicated osseous deformity. Middle phalanx >45°; soft-tissue deformity (polydactyly, macrodactyly)

*Clasped Thumb*

The clasped thumb represents a spectrum of thumb abnormalities, including (1) tightly adducted web at the first web space and deficiency of web-space skin, (2) severe flexion contracture of the metacarpophalangeal joint, often including volar subluxation, and (3) absent intrinsic muscles of opposition. The clasped thumb may be associated with ulnar-deviated fingers (i.e., windblown hand) and is often seen in conjunction with arthrogryposis, Freeman-Sheldon syndrome, or other syndromic conditions. This congenital flexion-adduction deformity was first classified by Weckesser et al.[103] in 1968 into four groups:

- Group I. Absent or weak function of the thumb extensor
- Group II. Absent or weak extension of the thumb and flexion contracture of fingers
- Group III. More complex thumb abnormalities, including thenar muscle hypoplasia and joint laxity or contracture
- Group IV. The above thumb abnormalities in addition to thumb duplication

Although this classification emphasized the spectrum of abnormalities, it did not prove clinically useful. McCarroll[104,105] presented a more practical two group classification in 1985, which was later extended by Mih in 1998[106] to specifically identify its occurrence in conjunction with other conditions (Type III). This descriptive scheme facilitates communication about this condition but provides limited information about treatment and prognosis.

- Type I. Supple. Absent or weak extension of the thumb.
- Type II. Complex. Hypoplastic or aplastic extensor tendons, fixed metacarpophalangeal joint flexion contracture, ulnar collateral ligament laxity, adduction-extension contractures of the carpometacarpal joint, absent or hypoplastic thenar muscles of opposition, or insufficient skin in the thumb-index web.
- Type III. Other conditions. The above-noted clasped-thumb abnormalities are associated with arthrogryposis, Freeman-Sheldon syndrome, or other syndromic conditions.

*Synostoses*

Three osseous synostoses have been classified on the basis of radiologic appearance; they have limited implications for surgery or prognosis.

**Proximal Radioulnar Synostoses**

Mital[107] presented a two-group classification system, which was later expanded by Cleary and Omer[108] to a four-group classification system.

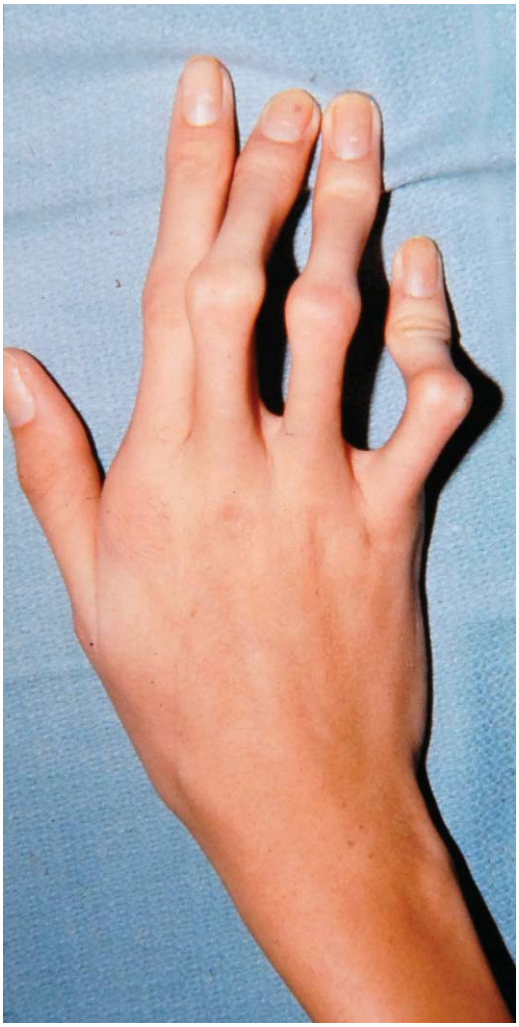

Fig. 7

Patient with severe camptodactyly of the little finger and less notable camptodactyly of the long and ring fingers.

- Type I. Clinical evidence of proximal radioulnar fusion without radiographic evidence (i.e., radioulnar syndesmosis)
- Type II. Osseous radioulnar synostosis, normal radial head
- Type III. Osseous radioulnar synostosis; posteriorly dislocated hypoplastic radial head
- Type IV. Osseous radioulnar synostosis; anteriorly dislocated radial head

**Lunotriquetral Coalition**

Carpal coalitions can occur between several bones in the proximal or distal carpal rows. However, only the lunotriquetral coalition has been classified[109].

- Type I. Incomplete fibrous or cartilaginous coalition
- Type II. Proximal synostosis, deep distal cleft
- Type III. Complete synostosis
- Type IV. Complete synostosis with other intercarpal fusions

**Fourth and Fifth Metacarpal Synostosis**

Wood's classification of the synostosis of the fourth and fifth metacarpals notes the skeletal abnormalities and the function of the little finger[110].

- Type I. Synostosis limited to the base of the fourth and fifth metacarpals; minimal functional limitations and deformity
- Type II. Synostosis of the proximal one-half of the fourth and fifth metacarpals; little finger hypoplastic, ulnar deviated
- Type III. Synostosis affecting more than half of the fourth and fifth metacarpals; metacarpal heads are separate, but fifth metacarpal is shortened and angled radially; little finger hypoplastic and abducted

## Group III: Duplication

This category includes classifications for radial polydactyly (including triphalangeal thumb), ulnar polydactyly, and ulnar dimelia (mirror hand). Central polydactyly has no detailed classifications; as noted above, its features are considered in conjunction with the central deficiency classification. Triphalangeal thumb is now included in radial polydactyly; interestingly, it was omitted from the original IFSSH classification scheme.

The developmental etiology of duplications is fairly well understood. In mice and chickens, ectopic anterior (radial) SHH increases limb volume and generates radial polydactyly, ranging from an extra digit to a complete mirror hand, and may further ulnarize the radius, yielding ulnar dimelia[111,112]. Mutations in the limb-specific SHH regulatory region are responsible for preaxial polydactyly or triphalangeal thumb[113,114]. Defects in Gli3, an antagonist of SHH, are linked to both radial and ulnar polydactyly, implicating overexpression of SHH in both forms of polydactyly[115]. However, polydactyly is likely more complicated than simple overexpression of SHH since mutations in a variety of other genes that appear unrelated to the SHH pathway are also linked to polydactyly.

***Radial Polydactyly***

The long-standing classification of thumb polydactyly (Fig. 8) was initially described by Wassel[116] in 1969, predating adoption of the current IFSSH classification system:

- Type I. Bifurcation at level of distal phalanx
- Type II. Bifurcation at level of interphalangeal joint
- Type III. Bifurcation at level of proximal phalanx
- Type IV. Bifurcation at level of metacarpophalangeal joint
- Type V. Bifurcation at level of metacarpal
- Type VI. Bifurcation at level of carpometacarpal joint
- Type VII. Triphalangeal thumb at level of metacarpophalangeal joint (variant of Type IV)

Wood[117] modified this classification to extend the description of the duplicated triphalangeal thumb. In contrast to Wassel, he noted the triphalangeal thumb occurred not only at the metacarpophalangeal joint (type IV), but also at the carpometacarpal joint. He modified the Wassel type-IV classifi-

cation to include the triphalangeal thumb as type IV-A and IV-B. Miura[118] later added type IV-C.

- Type IV-A. Both thumb components are triphalangeal at the metacarpophalangeal joint.
- Type IV-B. Only the radial component is triphalangeal at the metacarpophalangeal joint.
- Type IV-C. Only the ulnar component is triphalangeal at the metacarpophalangeal joint.

Wood also limited Type VII to triphalangeal thumb duplication at the carpometacarpal joint, which he further subclassified.

- Type VII-A. Radial component triphalangeal, ulnar component biphalangeal at the carpometacarpal joint
- Type VII-B. Both components triphalangeal at the carpometacarpal joint
- Type VII-C. Ulnar component triphalangeal, radial component biphalangeal at the carpometacarpal joint
- Type VII-D. Triple thumbs; central component triphalangeal, radial and ulnar components biphalangeal at the carpometacarpal joint

The Wassel classification, including the modifications by Wood and Miura, facilitates communication but does not consider important features such as relative size of the component parts, angulation of the phalanges, and presence of separate or common nail plates, which affect function, aesthetic appearance, and surgical decision-making.

Zuidam et al.[119] recently attempted to address some of these concerns with a more extended classification. This classification includes the carpal bones; type VII represents partial bifurcation at the level of the trapezium, and type VIII represents complete bifurcation at the scaphotrapezial joint. Additional features include specific notations for triphalangeal (Tph), triplication (T), symphalangism (S), deviation (D), and hypoplastic or floating (H); the directional positions of the deformities are assigned abbreviations: u (ulnar), m (middle), and r (radial). This classification may prove to be too complex to be useful, and does not provide information about treatment or prognosis.

### *Ulnar Polydactyly*

Ulnar polydactyly is manifested as a supernumerary digit on the ulnar side of the hand. The anomaly is classified according to the development of the digits[120].

- Type A. The supernumerary digit has well-developed little-finger soft-tissue and osseous structures, which articulate with the fifth metacarpal.
- Type B. The supernumerary digit is a rudimentary and pedunculated appendage attached to the ulnar side of the little finger or hand by a narrow skin bridge.

The classification provides both treatment guidelines and prognostic information, as type A is associated with syndromes in Caucasian patients.

### *Ulnar Dimelia (Mirror Hand)*

This condition represents a spectrum of presentations of duplication of the ulnar aspect of the embryonic limb bud.

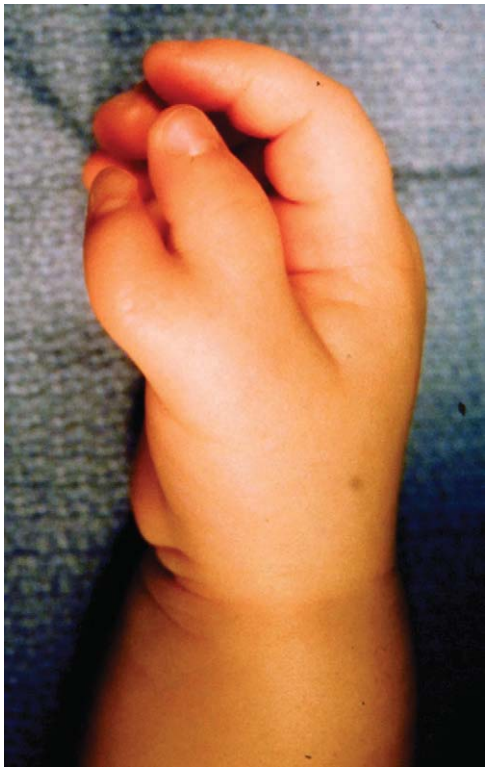

Fig. 8
Type-IV radial polydactyly.

The clinical features depend on the level of the duplication, ranging from duplication of the entire ulna at the elbow to duplication of the ulnar digits to form a six to eight-finger hand with no thumb. It is a rare and bizarre manifestation of duplication which is aesthetically unattractive and difficult to surgically reconstruct. The descriptive classification is based on the level of duplication[121] and does not guide treatment or provide prognosis.

- Type 1. Ulnar dimelia. Two ulnae with multiple fingers
- Type 1-A. Each ulna well formed
- Type 1-B. Preaxial ulna hypoplastic
- Type 2. Intermediate form. Two ulnae and a radius with multiple fingers
- Type 3. Intermediate form. One ulna and a radius with multiple fingers
- Type 3-A. Radius well formed
- Type 3-B. Radius hypoplastic
- Type 4. Syndromic form. Bilateral occurrence
- Type 4-A. Two ulnae
- Type 4-B. Ulna and radius
- Type 5. Multiple hand. Complete duplication of the hand, including the thumb; forearm normal

## Group IV: Overgrowth (Gigantism)

Macrodactyly is characterized by enlargement of osseous and various soft-tissue structures of one or more digits; extension of the enlargement into the wrist and entire

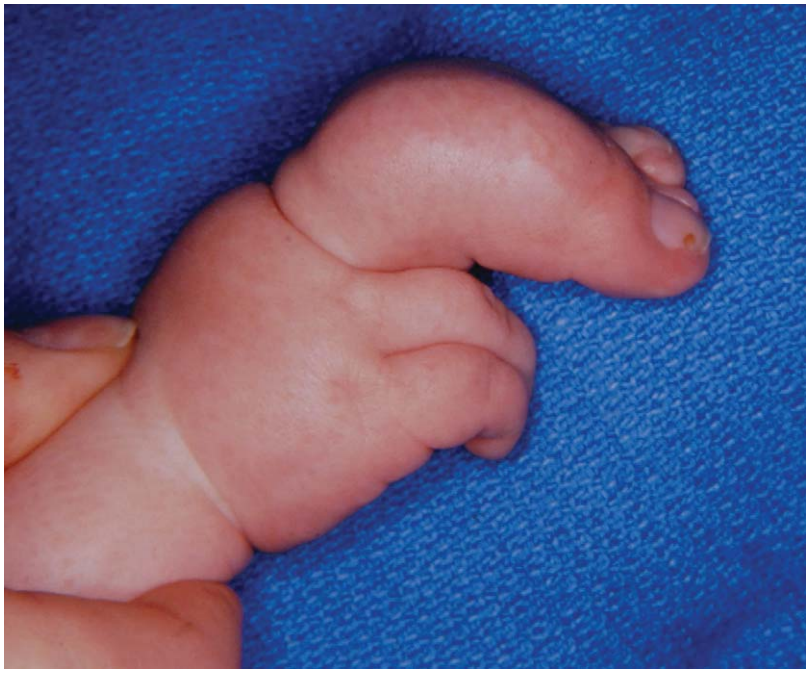

Fig. 9

Patient with type-I macrodactyly of the index and long digits, extending proximally into the hand.

upper extremity may be noted (Fig. 9). The digits may be angled, with stiff joints. Macrodactyly may be associated with various syndromes, including Ollier disease, Maffucci syndrome, Klippel-Trénaunay-Weber syndrome, and Proteus syndrome.

The classification is based on the underlying pathologic processes and does not reflect differences in appearance or guide surgical reconstruction[122].

- Type 1. Gigantism and lipofibromatosis. Enlarged fatty infiltrated nerves within the digit, extending proximally through the carpal tunnel. This is the most common form.
- Type 2. Gigantism and neurofibromatosis. Occurs in conjunction with plexiform neurofibromatosis; often bilateral. Enlarged osseous skeleton may be associated with osteochondral masses.
- Type 3. Gigantism and digital hyperostosis. Osteochondral periarticular masses that develop in infancy; no significant nerve enlargement; digits nodular and stiff; rare.
- Type 4. Gigantism and hemihypertrophy. Macrodactyly is a component of hemihypertrophy of the entire upper extremity. Intrinsic muscles abnormal or hypertrophic; all digits may be involved, including the thumb.

## Group V: Undergrowth (Hypoplasia)

See symbrachydactyly (central longitudinal deficiency-transverse) as noted above. There are no additional classifications in this category.

## Group VI: Congenital Constriction Band Syndrome

Ring constriction syndrome is characterized by bands that encircle the limbs at various levels. The bands can cause permanent indentation of the skin, local swelling, distal edema, syndactyly of adjacent and nonadjacent digits (usually with a proximal sinus), and terminal amputation. The syndrome is classified according to the severity of the presentation[123].

- Type 1. Simple constriction rings
- Type 2. Rings accompanied by distal soft-tissue deformity, with or without lymphedema
- Type 3. Distal osseous syndactyly
- Type 4. Terminal amputation

This classification is purely descriptive, and does not guide treatment or provide prognosis.

## Group VII: Generalized Skeletal Abnormalities

None of the congenital abnormalities in this category have been classified.

## Proposed Classification Modification Based on Molecular Biology

Based on our current understanding of limb development, several modifications to the IFSSH classification could be considered.

Since most of the conditions under failure of formation are deficiencies in axis formation or differentiation, it would be reasonable to group all of the following conditions involving axis disruption together in a *Failure of Axis Formation and/or Differentiation* category.

**TABLE II Proposed Modifications to the IFSSH Classification**

| |
|---|
| I. Failure of axis formation and/or differentiation |
| Radial longitudinal deficiency |
| Radial-ulnar synostosis |
| Ulnar longitudinal deficiency |
| Transverse deficiency (including symbrachydactyly) |
| Dorsal ventral deficiency |
| II. Failure of hand-plate formation and/or differentiation |
| Syndactyly |
| Apert syndrome |
| Central deficiency (cleft hand) |
| Camptodactyly |
| Clinodactyly |
| Clasped thumb |
| Hand-plate synostoses |
| Metacarpal synostosis |
| Carpal synostosis |
| III. Duplication |
| Radial polydactyly (including triphalangeal thumb) |
| Ulnar dimelia |
| Ulnar polydactyly |
| IV. Overgrowth |
| V. Amniotic band sequence |
| VI. Generalized skeletal abnormalities |

- Disruption of the radial-ulnar (anterior-posterior) axis either via loss of limb width, resulting in radial deficiencies, or a loss in posterior (ulnar) patterning, leading to ulnar deficiencies
- Disruption of the proximal-distal axis, resulting in transverse deficiencies
- Disruption of the dorsal-ventral axis, causing nail-patella syndrome and palmar nail syndrome

In addition, synostoses involving the radius and ulna seem to be more related to longitudinal deficiencies and thus would necessitate a shift to the failure of axis formation and/or differentiation category. Furthermore, symbrachydactyly has recently been linked to a disruption in Wnt signaling and, as such, is consistent with a form of transverse deficiency[91]; it should be placed in the failure of axis formation and/or differentiation category, eliminating the undergrowth category.

Failure of differentiation is a somewhat vague term that does not really reflect the conditions that have been grouped under this category. A term that may better represent most of these entities is failure of hand-plate development and/or differentiation. This category would include developmental malformations targeting the hand. Therefore, shifting central deficiency to this category would be appropriate. Furthermore, since recent work indicates that similar misregulation or ectopic expression of SHH induces both radial polydactyly and triphalangeal thumb[113,114], it would be reasonable to include triphalangeal thumb in the radial polydactyly subcategory of failure of hand-plate development and/or differentiation.

The proposed modification is shown in Table II. It reflects the basic concepts of the original IFSSH classification but includes the current understanding of limb development. We recommend it to congenital hand surgeons for their consideration.

## Conclusions

The IFSSH classification has provided a useful framework for congenital upper-extremity anomalies for over forty years, accommodating specific classifications for twenty different conditions within its seven categories. As detailed above, few of these classification schemes live up to the ideal, which is to guide treatment, provide insight into prognosis, or incorporate the etiologic mechanism of the condition. Recent developments in molecular biology allow us to propose a modification to the IFSSH classification to incorporate our enhanced understanding of the etiology of congenital malformations. The ideal classification scheme awaits further investigation. ■

Paul R. Manske, MD
Washington University School of Medicine,
Campus Box 8233, 660 South Euclid Avenue,
St. Louis, MO 63110. E-mail address:
manskep@wudosis.wustl.edu

Kerby C. Oberg, MD, PhD
Divisions of Pediatric Pathology and Human Anatomy,
Department of Surgery, Loma Linda University,
24785 Stewart Street, Room B09c,
Loma Linda, CA 92350

## References

**1.** Daluiski A, Yi SE, Lyons KM. The molecular control of upper extremity development: implications for congenital hand anomalies. J Hand Surg [Am]. 2001;26:8-22.

**2.** Kawakami Y, Capdevila J, Buscher D, Itoh T, Rodríguez Esteban C, Izpisúa Belmonte JC. WNT signals control FGF-dependent limb initiation and AER induction in the chick embryo. Cell. 2001;104:891-900.

**3.** Panman L, Zeller R. Patterning the limb before and after SHH signalling. J Anat. 2003;202:3-12.

**4.** Chen H, Johnson RL. Interactions between dorsal-ventral patterning genes lmx1b, engrailed-1 and wnt-7a in the vertebrate limb. Int J Dev Biol. 2002;46:937-41.

**5.** Kawakami Y, Wada N, Nishimatsu S, Nohno T. Involvement of frizzled-10 in Wnt-7a signaling during chick limb development. Dev Growth Differ. 2000;42:561-9.

**6.** Summerbell D. A quantitative analysis of the effect of excision of the AER from the chick limb-bud. J Embryol Exp Morphol. 1974;32:651-60.

**7.** Lu P, Yu Y, Perdue Y, Werb Z. The apical ectodermal ridge is a timer for generating distal limb progenitors. Development. 2008;135:1395-405.

**8.** Yu K, Ornitz DM. FGF signaling regulates mesenchymal differentiation and skeletal patterning along the limb bud proximodistal axis. Development. 2008;135:483-91.

**9.** Towers M, Mahood R, Yin Y, Tickle C. Integration of growth and specification in chick wing digit-patterning. Nature. 2008;452:882-6.

**10.** Zhu J, Nakamura E, Nguyen MT, Bao X, Akiyama H, Mackem S. Uncoupling Sonic hedgehog control of pattern and expansion of the developing limb bud. Dev Cell. 2008;14:624-32.

**11.** Buck-Gramcko D. Congenital malformation in hand surgery. In: Nigst H, Buck-Gramcko D, Millesi H, Lister GD, editors. Hand surgery. New York: Thieme Medical Publishers; 1988. p 12.1-12.110.

**12.** Kay H. A proposed international terminology for the classification of congenital limb deficiencies. Orthotics Prosthetics. 1974;28:33-48.

**13.** Kelikian H. Congenital deformities of the hand and forearm. Philadelphia: WB Saunders; 1974. Classifications; p 51-88.

**14.** Saint-Hilaire IG. Propositions sur la monstruosité. Paris: Imp. Didot le Jeune; 1829. p 18-9.

**15.** Otto AW. A compounding of human comparative pathological anatomy. London: B Fellows; 1831. p 1-41, 216-20.

**16.** Saint-Hilaire IG. Histoire générale et particulière des anomalies de l'organisation chez l'homme et les animaux. Paris: JB Baillière; 1832. p 257-78, 670-702.

**17.** Fort AJ. Des difformités congénitales et acquises des doigts, et des moyens d'y remédier. Paris: Adrien Delahaye; 1869. p 8-11.

**18.** Leboucq J. Recherches sur la morphologie du carpe chez les mammifères. Arch Biol. 1884;5:35-102.

**19.** Polaillon JF. Doigt. In: Dechambre K, editor. Dictionnaire encyclopédique des sciences médicales. Paris: G Masson and P Asselin; 1884. p 115-353.

**20.** Potel G. Essai sur les malformations congénitales des membres. Leur classification pathogénique. Rev Chir. 1914;49:293-326, 625-48, 822-58; 50: 84-114.

**21.** Frantz C, O'Rahilly R. Congenital skeletal limb deficiencies. J Bone Joint Surg Am. 1961;43:1202-24.

**22.** O'Rahilly R. Morphological patterns in limb deficiencies and duplications. Am J Anat. 1951;89:135-94.

**23.** Kümmel W. Die Missbildungen der Extremitaeten durch Defekt, Verwachsung und Ueberzahl. Cassel, Germany: TG Fischer; 1895. p 1-83.

**24.** Nigst PF. Über kongenitale Missbildungen des menschlichen Extremitätenskeletts, mit Röntgenbildern. Schweiz Med Wschr. 1927;8:7-18, 53-61, 81-91, 97-106.

**25.** Müller W. Die Angeborenen Fehlbildungen der menschlichen Hand. Leipzig: Thieme; 1937.

**26.** Swanson AB. A classification for congenital malformations of the hand. Bull Acad Med N J. 1964;10:166-9.

**27.** Swanson AB, Barsky AJ, Entin MA. Classification of limb malformations on the basis of embryological failures. Surg Clin N Amer. 1968;48:1169-79.

**28.** Swanson AB. A classification for congenital limb malformations. J Hand Surg [Am]. 1976;1:8-22.

**29.** Baruch AD, Hecht OA. Treatment of monodactyly by the distraction-lengthening principle: a case report. J Hand Surg [Am]. 1983;8(5 Pt 1):604-6.

**30.** Buckwalter JA, Flatt AE, Shurr DG, Dryer RF, Blair WF. The absent fifth metacarpal. J Hand Surg [Am]. 1981;6:364-7.

**31.** Kato S, Ishii S, Ogino T, Shiono H. Anomalous hands with cleft formation between the fourth and fifth digits. J Hand Surg [Am]. 1983;8:909-13.

**32.** Light TR, Ogden JA. The longitudinal epiphyseal bracket: implications for surgical correction. J Pediatr Orthop. 1981;1:299-305.

**33.** Miura T. Cleft hand involving only the ring and small fingers. J Hand Surg [Am]. 1988;13:530-5.

**34.** Cheng JC, Chow SK, Leung PC. Classification of 578 cases of congenital upper limb anomalies with the IFSSH system—a 10 years' experience. J Hand Surg [Am]. 1987;12:1055-60.

**35.** Knight SL, Kay SPJ. Classification of congenital anomalies. In: Gupta A, Kay SPJ, Scheker LR, editors. The growing hand: diagnosis and management of the upper extremity in children. London: Mosby; 2000. p 125-35.

**36.** Congenital Hand Committee of the JSSH. Modified IFSSH classification. J Japan Soc Surg Hand. 2000;17:353-65.

**37.** Kato H, Ogino T, Minami A, Ohshio I. Experimental study of radial ray deficiency. J Hand Surg [Br]. 1990;15:470-6.

**38.** Ogino T, Kato H. Clinical and experimental studies on ulnar ray deficiency. Handchir Mikrochir Plast Chir. 1988;20:330-7.

**39.** Tonkin MA. Description of congenital hand anomalies: a personal view. J Hand Surg [Br]. 2006;31:489-97.

**40.** Goldfarb CA, Manske PR, Busa R, Mills J, Carter P, Ezaki M. Upper-extremity phocomelia reexamined: a longitudinal dysplasia. J Bone Joint Surg Am. 2005;87: 2639-48.

**41.** Tytherleigh-Strong G, Hooper G. The classification of phocomelia. J Hand Surg [Br]. 2003;28:215-7.

**42.** Mariani FV, Ahn CP, Martin GR. Genetic evidence that FGFs have an instructive role in limb proximal-distal patterning. Nature. 2008;453:401-5.

**43.** Sun X, Mariani FV, Martin GR. Functions of FGF signalling from the apical ectodermal ridge in limb development. Nature. 2002;418:501-8.

**44.** Goldfarb CA, Wall L, Manske PR. Radial longitudinal deficiency: the incidence of associated medical and musculoskeletal conditions. J Hand Surg [Am]. 2006; 31:1176-82.

**45.** Blauth W. Der hypoplastische Daumen. Arch Orthop Unfallchir. 1967;62:225-46.

**46.** James MA, McCarroll HR Jr, Manske PR. Characteristics of patients with hypoplastic thumbs. J Hand Surg [Am]. 1996;21:104-13.

**47.** Manske PR, McCarroll HR Jr, James M. Type III-A hypoplastic thumb. J Hand Surg [Am]. 1995;20:46-53.

**48.** Graham TJ, Louis DS. A comprehensive approach to surgical management of the type IIIA hypoplastic thumb. J Hand Surg [Am]. 1998;23:3-13.

**49.** Bayne LG, Klug MS. Long-term review of the surgical treatment of radial deficiencies. J Hand Surg [Am]. 1987;12:169-79.

**50.** James MA, McCarroll HR Jr, Manske PR. The spectrum of radial longitudinal deficiency: a modified classification. J Hand Surg [Am]. 1999;24: 1145-55.

**51.** Nutt JN 3rd, Flatt AE. Congenital central hand deficit. J Hand Surg [Am]. 1981;6:48-60.

**52.** Ogino T. Cleft hand. Hand Clin. 1990;6:661-71.

**53.** Tada K, Yonenobu K, Swanson AB. Congenital central ray deficiency in the hand—a survey of 59 cases and subclassification. J Hand Surg [Am]. 1981;6:434-41.

**54.** Watari S, Tsuge K. A classification of cleft hands, based on clinical findings: theory of developmental mechanism. Plast Reconstr Surg. 1979;64:381-9.

**55.** Lo Iacono N, Mantero S, Chiarelli A, Garcia E, Mills AA, Morasso MI, Costanzo A, Levi G, Guerrini L, Merlo GR. Regulation of Dlx5 and Dlx6 gene expression by p63 is involved in EEC and SHFM congenital limb defects. Development. 2008; 135:1377-88.

**56.** Duijf PH, van Bokhoven H, Brunner HG. Pathogenesis of split-hand/split-foot malformation. Hum Mol Genet. 2003;12 Spec No 1:R51-60.

**57.** Buck-Gramcko D. Cleft hands: classification and treatment. Hand Clin. 1985; 1:467-73.

**58.** Ogino T. Teratogenic relationship between polydactyly, syndactyly and cleft hand. J Hand Surg [Br]. 1990;15:201-9.

**59.** Naruse T, Takahara M, Takagi M, Oberg KC, Ogino T. Busulfan-induced central polydactyly, syndactyly and cleft hand or foot: a common mechanism of disruption leads to divergent phenotypes. Dev Growth Differ. 2007;49:533-41.

**60.** Barsky AJ. Cleft hand: classification, incidence, and treatment. Review of the literature and report of nineteen cases. J Bone Joint Surg Am. 1964;46: 1707-20.

**61.** Flatt AE. The care of congenital hand anomalies. St. Louis: Mosby; 1977. p 328-41.

**62.** Ogino T, Minami A, Kato H. Clinical features and roentgenograms of symbrachydactyly. J Hand Surg [Br]. 1989;14:303-6.

**63.** Sandzen SC Jr. Classification and functional management of congenital central defect of the hand. Hand Clin. 1985;1:483-98.

**64.** Flatt AE. The care of congenital hand anomalies. St. Louis: Mosby; 1977. p 265-85.

**65.** Manske PR, Halikis MN. Surgical classification of central deficiency according to the thumb web. J Hand Surg [Am]. 1995;20:687-97.

**66.** Sykes PJ, Eadie PA. Longitudinal ulnar deficiency in the hand. In: Gupta A, Kay SPJ, Scheker LR, editors. The growing hand: diagnosis and management of the upper extremity in children. London: Mosby; 2000. p 189-95.

**67.** Bayne LG. Ulnar club hand (ulnar deficiencies). In: Green DP, editor. Operative hand surgery. New York: Churchill Livingstone; 1982. p 245-57.

**68.** Miller JK, Wenner SM, Kruger LM. Ulnar deficiency. J Hand Surg [Am]. 1986;11:822-9.

**69.** Ogden JA, Watson HK, Bohne W. Ulnar dysmelia. J Bone Joint Surg Am. 1976;58:467-75.

**70.** Riordan DC. The upper limb. In: Lowell WW, Lovell RB, Winter RB, editors. Pediatric orthopaedics. Vol 2. Philadelphia: JB Lippincott; 1978. p 685-719.

**71.** Swanson AB, Tada K, Yonenobu K. Ulnar ray deficiency: its various manifestations. J Hand Surg [Am]. 1984;9:658-64.

**72.** Havenhill TG, Manske PR, Patel A, Goldfarb CA. Type 0 ulnar longitudinal deficiency. J Hand Surg [Am]. 2005;30:1288-93.

**73.** Blair WF, Shurr DG, Buckwalter JA. Functional status in ulnar deficiency. J Pediatr Orthop. 1983;3:37-40.

**74.** Broudy AS, Smith RJ. Deformities of the hand and wrist with ulnar deficiency. J Hand Surg [Am]. 1979;4:304-15.

**75.** Carroll RE, Bowers WH. Congenital deficiency of the ulna. J Hand Surg [Am]. 1977;2:169-74.

**76.** Cole RJ, Manske PR. Classification of ulnar deficiency according to the thumb and first web. J Hand Surg [Am]. 1997;22:479-88.

**77.** Johnson J, Omer GE Jr. Congenital ulnar deficiency. Natural history and therapeutic implications. Hand Clin. 1985;1:499-510.

**78.** Buchler U. Symbrachydactyly. In: Gupta A, Kay SPJ, Scheker LR, editors. The growing hand: diagnosis and management of the upper extremity in children. London: Mosby; 2000. p 213-24.

**79.** Erhardt PR, Lindley SG, Functional development of the hand. In: Gupta A, Kay SPJ, Scheker LR, editors. The growing hand: diagnosis and management of the upper extremity in children. London: Mosby; 2000. p 71-82.

**80.** James M, Bednar M. Deformities of the wrist and forearm. In: Green DP, Hotchkiss RN, Pederson WC, Wolfe SW, editors. Green's operative hand surgery. 5th ed. Philadelphia: Elsevier Churchill Livingstone; 2005. p 1489-91.

**81.** Kay SP. Congenital hand deformities: hypoplastic and absent digits. In: Green DP, Hotchkiss RN, Pederson WC, editors. Green's operative hand surgery. 4th ed, vol 1. New York: Churchill Livingstone; 1998. p 368-75.

**82.** Kay SP, McCombe D, Kozin SH. Deformities of the hand and fingers. In: Green DP, Hotchkiss RN, Pederson WC, Wolfe SW, editors. Green's operative hand surgery. 5th ed. Philadelphia: Elsevier Churchill Livingstone; 2005. p 1417-30.

**83.** Light TR. Congenital anomalies: syndactyly, polydactyly, and cleft hand. In: Peimer CA, editor. Surgery of the hand and upper extremity. New York: McGraw-Hill; 1996. p 2121-3.

**84.** Tonkin MA. Congenital hand deformities: major limb defects. In: Green DP, Hotchkiss RN, Pederson WC, editors. Green's operative hand surgery. 4th ed, vol 1. New York: Churchill Livingstone; 1998. p 338-41.

**85.** Waters PM, Simmons BP. Congenital anomalies: elbow region. In: Peimer CA, editor. Surgery of the hand and upper extremity. New York: McGraw-Hill; 1996. p 2050-1.

**86.** Blauth W, Gekeler J. [Morphology and classification of symbrachydactylia]. Handchirurgie. 1971;3:123-8. German.

**87.** Buck-Gramcko D. Symbrachydactyly: a clinical entity. Tech Hand Up Extrem Surg. 1999;3:242-58.

**88.** Yamauchi Y, Tanabu S. Symbrachydactyly. In: Buck-Gramcko D, editor. Congenital malformations of the hand and forearm. Philadelphia: Churchill Livingstone; 1998. p 149-58.

**89.** Kallemeier PM, Manske PR, Davis B, Goldfarb CA. An assessment of the relationship between congenital transverse deficiency of the forearm and symbrachydactyly. J Hand Surg [Am]. 2007;2:1408-12.

**90.** Summerbell D, Lewis JH. Time, place and positional value in the chick limb-bud. J Embryol Exp Morphol. 1975;33:621-43.

**91.** Winkel A, Stricker S, Tylzanowski P, Seiffart V, Mundlos S, Gross G, Hoffmann A. Wnt-ligand-dependent interaction of TAK1 (TGF-beta-activated kinase-1) with the receptor tyrosine kinase Ror2 modulates canonical Wnt-signalling. Cell Signal. 2008;20:2134-44.

**92.** Pol R. 'Brachydaktylie'—'Klinodaktylie'—Hyperphalangie und ihre Grundlagen: Form und Entstehung der meist unter dem Bild der Brachydaktylie auftretenden Varietäten, Anomalien und Mißbildungen der Hand und des Fußes. Virchows Arch Path Anat. 1921;229:388-530.

**93.** Kelikian H. Congenital deformities of the hand and forearm. Philadelphia: WB Saunders; 1974. Phocomelia; p 891-901.

**94.** Merino R, Rodriguez-Leon J, Macias D, Gañan Y, Economides AN, Hurle JM. The BMP antagonist Gremlin regulates outgrowth, chondrogenesis and programmed cell death in the developing limb. Development. 1999;126: 5515-22.

**95.** Weatherbee SD, Behringer RR, Rasweiler JJ 4th, Niswander LA. Interdigital webbing retention in bat wings illustrates genetic changes underlying amniote limb diversification. Proc Natl Acad Sci U S A. 2006;103: 15103-7.

**96.** Pajni-Underwood S, Wilson CP, Elder C, Mishina Y, Lewandoski M. BMP signals control limb bud interdigital programmed cell death by regulating FGF signaling. Development. 2007;134:2359-68.

**97.** Flatt AE. The care of congenital hand anomalies. St. Louis: Mosby; 1977. p 170-92.

**98.** Dobyns JH. Syndactyly. In: Green DP, Hotchkiss RN, Pederson WC, editors. Green's operative hand surgery. 3rd ed. New York: Churchill Livingstone; 1993. p 346.

**99.** Upton J. Apert syndrome. Classification and pathologic anatomy of limb anomalies. Clin Plast Surg. 1991;18:321-55.

**100.** Van Heest AE, House JH, Reckling WC. Two-stage reconstruction of Apert acrosyndactyly. J Hand Surg [Am]. 1997;22:315-22.

**101.** Benson LS, Waters PM, Kamil NI, Simmons BP, Upton J 3rd. Camptodactyly: classification and results of nonoperative treatment. J Pediatr Orthop. 1994; 14:814-9.

**102.** Cooney WP. Camptodactyly and clinodactyly. In: Carter PR, editor. Reconstruction of the child's hand. Philadelphia: Lea and Febiger; 1991. p 209-35.

**103.** Weckesser EC, Reed JR, Heipel KG. Congenital clasped thumb (congenital flexion-adduction deformity of the thumb): a syndrome, not a specific entity. J Bone Joint Surg Am. 1968;50:1417-28.

**104.** McCarroll HR Jr. Congenital flexion deformities of the thumb. Hand Clin. 1985;1:567-75.

**105.** McCarroll HR Jr, Manske PR. The windblown hand: correction of the complex clasped thumb deformity. Hand Clin. 1992;8:147-59.

**106.** Mih AD. Congenital clasped thumb. Hand Clin. 1998;14:77-84.

**107.** Mital MA. Congenital radioulnar synostosis and congenital dislocation of the radial head. Orthop Clin North Am. 1976;7:375-83.

**108.** Cleary JE, Omer GE Jr. Congenital proximal radio-ulnar synostosis. Natural history and functional assessment. J Bone Joint Surg Am. 1985;67: 539-45.

**109.** Minnaar A. Congenital fusion between the lunate and the triquetral bones in the South African Bantu. J Bone Joint Surg Br. 1952;34:45-8.

**110.** Wood VE. Metacarpal synostosis. In: Green DP, Hotchkiss RN, Pederson WC, editors. Green's operative hand surgery. 3rd ed. New York: Churchill Livingstone; 1993. p 326-38.

**111.** Charité J, de Graaff W, Shen S, Deschamps J. Ectopic expression of Hoxb-8 causes duplication of the ZPA in the forelimb and homeotic transformation of axial structures. Cell. 1994;78:589-601.

**112.** Yang Y, Drossopoulou G, Chuang PT, Duprez D, Marti E, Bumcrot D, Vargesson N, Clarke J, Niswander L, McMahon A, Tickle C. Relationship between dose, distance and time in Sonic Hedgehog-mediated regulation of anteroposterior polarity in the chick limb. Development. 1997;124:4393-404.

**113.** Lettice LA, Heaney SJ, Purdie LA, Li L, de Beer P, Oostra BA, Goode D, Elgar G, Hill RE, de Graaff E. A long-range Shh enhancer regulates expression in the developing limb and fin and is associated with preaxial polydactyly. Hum Mol Genet. 2003;12:1725-35.

**114.** Gurnett CA, Bowcock AM, Dietz FR, Morcuende JA, Murray JC, Dobbs MB. Two novel point mutations in the long-range SHH enhancer in three families with triphalangeal thumb and preaxial polydactyly. Am J Med Genet A. 2007;143: 27-32.

**115.** Radhakrishna U, Bornholdt D, Scott HS, Patel UC, Rossier C, Engel H, Bottani A, Chandal D, Blouin JL, Solanki JV, Grzeschik KH, Antonarakis SE. The phenotypic spectrum of GLI3 morphopathies includes autosomal dominant pre-

axial polydactyly type-IV and postaxial polydactyly type-A/B; no phenotype prediction from the position of GLI3 mutations. Am J Hum Genet. 1999;65:645-55.

**116.** Wassel HD. The results of surgery for polydactyly of the thumb. Clin Orthop Relat Res. 1969;64:175-93.

**117.** Wood VE. Polydactyly and the triphalangeal thumb. J Hand Surg [Am]. 1978;3:436-44.

**118.** Miura T. Triphalangeal thumb. Plast Reconstr Surg. 1976;58:587-94.

**119.** Zuidam JM, Selles RW, Ananta M, Runia J, Hovius SE. A classification system of radial polydactyly: inclusion of triphalangeal thumb and triplication. J Hand Surg [Am]. 2008;33:373-7.

**120.** Temtamy S, McKusick VA. Synopsis of hand malformations with particular emphasis on genetic factors. Birth Defects. 1969;5:125-84.

**121.** Al-Qattan MM, Al-Thunayan A, De Cordier M, Nandagopal N, Pitkanen J. Classification of the mirror hand-multiple hand spectrum. J Hand Surg [Br]. 1998;23:534-6.

**122.** Flatt AE. The care of congenital hand anomalies. 2nd ed. St. Louis, MO: Quality Medical Publishing; 1994. p 317-33.

**123.** Patterson TJ. Congenital ring-constrictions. Br J Plast Surg. 1961;14:1-31.