Plastic and Reconstructive Surgery

Wei Wang
Jianmin Yao
Editors

Congenital Deformities of the Hand and Upper Limb

Springer

Plastic and Reconstructive Surgery

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Profile of Chief Editors of *Congenital Deformities of Hands and Upper Limbs*

Wei Wang Wang Wei is a tenured professor of plastic surgery and one of the founders of the Chinese Plastic and Reconstructive Surgery Association and Plastic Surgery Branch of the Chinese Medical Doctor Association as well as an international editorial board member of *Plastic and Reconstructive Surgery*. He has successively served as chairman, vice chairman, member of standing committee, associate editor, and editorial board member of over 30 associations and journals at home and abroad.

He started his career in plastic surgery with a master's degree in 1961. When he was a senior in college, he was elected as a physician of the Cardiology Department of Shanghai Ruijin Hospital and has been in charge of 26 sickbeds for half a year. From1981 to 1982, he was a visiting scholar and visiting professor at Baylor College of Medicine in the United States. Since 1967, he has served as the discipline leader, deputy director (executive) and director, and leader of Shanghai's key medical disciplines as well as an academic leader of the "211 Project" for the Ministry of Education.

He reported and published over 40 leading achievements at home and abroad. For example, in 1965, he reported *An Experimental Study on Free Replantation of Skin Tissues*. In 1975, he applied the dorsal island flap grafting and free grafting. In 1977, he performed cervical esophageal reconstruction with a free jejunum flap and a jejunum-esophagus grafting as well as cervical and thoracic esophageal reconstruction with a proximal jejunal pedicle and a distal anastomosis grafting. In 1985, he was hailed as the "world's most experienced doctor in esophageal reconstruction with intestinal grafting" by American scholars. In 1990, he created cervical esophageal reconstruction with the pectoral musculoskin flap grafting. In 1991, he created cervical esophageal reconstruction with the tubular latissimus dorsi flap. In 1977, he expanded this technique to second-toe transplantation. In 1979, he created a treatment for postburn claw hand with the superficial temporal fascia flap and skin grafting. That year, he also performed island skin flap grafting in the medial plantar and of the metatarsophalangeal joint flap grafting with a 0.8 cm × 5.0 cm area of skin, nerves, and blood vessels, which were used for hand or temporomandibular joint reconstruction. In 1980, he and Yang Guofan reported a free forearm flap grafting. In 1980, he proposed in *Medical Encyclopedia* that the free forearm flap grafting be used for cervical esophageal or penile reconstruction, creating the grafting of the reversed forearm island flap. In 1982, he reported the etiology and classification of lymphedema. In the same year, he created the treatment of traumatic anal sphincter reconstruction with the greatest gluteal muscle flap grafting and subsequently used it for anal sphincter reconstruction to treat colorectal cancer in situ. In 1985, he created Y-shaped microvascular anastomosis method. In 1989, he reported the treatment for advanced facial nerve paralysis with the grafting of free latissimus dorsi muscle (Phase I). In 1995, he performed treatment for advanced facial nerve paralysis (Phase I) with the grafting of the latissimus dorsi muscle free flap. He has many innovative achievements in classification of thumb dysplasia, aesthetic reconstruction, modern

abdominoplasty, augmentation mammoplasty with prosthetics, facial contour beautification, eyelid and nasal surgery, and other fields. Since 1984, he has been engaged in the practice of "plastic surgery" and "cosmetic surgery."

He prepared the *Rules for Training Chinese Orthopedic Surgeons* and *Rules for the Scope and Classification of Plastic Surgeries* for the competent department. The majority of surgeons under his guidance have become academic leaders of provinces and municipalities. He also trained over 20 professors and surgeons for the United States, the United Kingdom, Italy, and other countries.

He has won the National Invention Award for over 20 times. He is listed in the *History of Microsurgery* and *Who's Who* as a medical celebrity.

Jianmin Yao Yao Jianmin, a chief physician, was awarded the title "Top 10 Young Doctors" in Hangzhou in 1991. In 1982, he graduated from the Hangzhou Campus of Zhejiang Medical University. Currently, he is an academic leader in Hangzhou's medical hand surgery key specialties, a standing committee member of the Hand Surgery Branch for Zhejiang Medical Association, a member of the Plastic Surgery Branch of Zhejiang Medical Association, vice chairman of the Limb Function Reconstruction Professional Committee for Zhejiang Provincial Rehabilitation Medicine Association, and the seventh and eighth special editorial member of the *Chinese Journal of Microsurgery*.

He has published 49 academic papers, including 11 SCI papers. In 1997, he published the "Treatment of Simple Syndactyly by Reverse Insertion Method of Webbed Fascia Pedicle Skin Flap" in the journal *Plastic and Reconstructive Surgery*. Currently, he has published 22 papers in first-class Chinese journals and12 papers that won awards. He has won first, second, and third prizes via his excellent papers at municipal, provincial, and national meetings.

His research "Breast Splitters for Mammoplasty" won a national patent. He completed nine research projects independently or by cooperating with others, which have reached a leading level at home and abroad. In addition, he has won the first, second, and third prizes of science and technology awards at the municipal level, at the provincial level, and of the Ministry of Health, respectively. In 1995, the project *Repair of Acute Thumb Avulsion with Bi-lobed Island Flap of the Second Web* won the third prize of the Zhejiang Provincial Science and Technology Progress Award. In 1997, the project *Microanatomy Research and Clinical Applications of Hand and Forearm Island Flaps* won the third prize of the Ministry of Health and the first prize of Hangzhou Science and Technology Progress Award. In 2006, he compiled the *Atlas of Clinical Surgery for Flap Repair of Hand and Foot Wounds.* In 1997, he studied at the Beckman Laser Institute & Medical Clinic of the University of California in the United States. In September 2007, he went to Luisenhospital Aachen in Germany for an exchange program. In 1997, he was listed as a third-level talent in Hangzhou Talent Education Training.

Editorial Board of *Congenital Deformities of Hands and Upper Limbs*

Preface

Congenital anomaly of the hand and upper limb is a common disease. Patients with such a disease can pay a visit to a department of plastic surgery, department of pediatric surgery, department of hand surgery, department of orthopedic surgery, or department of general surgery. Therefore, it is necessary for healthcare providers to know and be familiar with this type of disease as well as its treatment.

In 1986, in the first National Symposium and Workshop of Hand Surgery held in Qingdao, the author presented the report *Classification of Congenital Hand and Upper Limb Deformities*. Thereafter, lectures on congenital deformities of the hand and upper limbs were delivered in Shanghai, Guangzhou, Beijing, Wuhan, and other places. In *Huang Jiasi Surgery* and *Plastic Surgery*, of which the author is the chief editor (1999), relevant chapters on congenital deformities of the hand and upper limbs were written. In 2004, with the assistance of the author, Professor Hong Guangxiang compiled and published *Congenital Deformities of Hands.* The book *Congenital Deformities of Hands and Upper Limbs* has been written and published based on them.

The author had the honor to invite professors and scholars in plastic surgery, hand surgery, and orthopedics from North and South China as well as in the Hand Surgery Center at University of Louisville Hospital to participate in the composition and compilation of *Congenital Deformities of the Hand and Upper Limb.* It took more than 2 years to finish the book.

During the compilation process, the authors summarized their decades of experiences and reviewed hundreds of thousands of pictures of hand deformities. In addition, they referred to over a thousand articles and books on congenital deformities of hands and upper limbs published at home and abroad.

In clinical practice, there appears to be many malpractice cases in the treatment of congenital deformities of hands and upper limbs, most of which are caused by a lack of understanding of the morphological, structural, and functional defects of hand deformities as well as inappropriate selection of treatment measures. Therefore, only when the morphological, structural, and functional defects of hand deformities are fully understood can the best therapeutic regimen be generated. To this end, hand examination method and hand function assessment method have been added to this book. Professor Tsai from the Hand Surgery Center of University of Louisville Hospital in the United States actively participated in the compilation of this book, for which the author is deeply grateful.

Although every effort has been made to compose and compile this book, shortcomings are inevitable, so any feedback is welcome.

Shanghai, China
October 18, 2014

Wei Wang

Acknowledgments

During the compilation of *Congenital Deformities of Hands and Upper Limbs*, the editors have contacted professors from famous hand surgery centers in the United States for many times, and Professor Tsai and Professor Tien from US Kleinert Kutz Hand Surgery Center have taken an active part in our compilation and made amendments and supplements to relevant chapters. We are very glad to have American peers participate in the compilation of this book, and they will be introduced as follows.

It has been over 50 years since US Kleinert Kutz Hand Surgery Center was founded, and it has a large number of famous surgeons and scholars in hand surgery. This center is currently one of the world's largest training bases of hand surgeons. From 1960 to now, a total of over 1200 surgeons from 58 countries have received professional training in the field of hand surgery here. This center owns medical bases in Louisville and Lexington in Kentucky and New Albany in Indiana, and it provides comprehensive medical services in upper limbs for patients from all over the world. During the past over five decades, Kleinert Kutz Hand Surgery Center has performed seven allogenic hand transplantations and the world's first batch of hand replantations. It has been the cutting edge in the field of free tissue transplantation and reconstruction; its research in peripheral nerve blood supply has won national honors; it is the first to report finger arterial repair, bilateral upper arm replantation, bilateral forearm replantation, and vascularized epiphysis transplantation; and it has successfully created a set of techniques in flexor tendon repair and rehabilitation.

Tsu-Min Tsai (M.D.) is a renowned specialist in hand surgery and microsurgery. Dr. Tsai once performed replantation of amputated finger for Armstrong, the one who first landed on the moon. Dr. Tsai graduated from National Taiwan University in 1961 and received the training of National Taiwan University and University of Louisville Hospital. Dr. Tsai acted as chief of surgery in Taipei Peace Hospital from 1970 to 1975. In 1976, Dr. Tsai received training at Kleinert Kutz Hand Surgery Center. Currently, Dr. Tsai is the clinical professor in orthopedics in University of Louisville Hospital, a member of the American Society for Reconstructive Microsurgery, a member of the World Society for Reconstructive Microsurgery, and an official member of the American Association for Hand Surgery. Dr. Tsai has been devoted to the clinical and research work in the field of hand surgery and microsurgery and has published a total of over 130 articles.

Huey Y. Tien (M.D.) is a renowned specialist in hand surgery and microsurgery and has treated patients with injuries in wrist joint and brachial plexus from all over the world. Dr. Tien graduated from Chung Shan Medical College in 1986. He completed the training for resident orthopedist in Taoyuan Armed Forces General Hospital and the training for resident surgeon in University of Louisville Hospital. In the last year, Dr. Tien acted as the chief resident and subsequently received specialized training in hand surgery in Kleinert Kutz Hand Surgery Center. Currently, Dr. Tien is clinical associate professor of University of Louisville Hospital, official member of the American Association for Hand Surgery and official member of the Association for the Study of Internal Fixation, and also director of Surgeon Training Department of Kleinert Kutz Hand Surgery Center.

Special thanks should go to Dr. Han Dong from the Department of Plastic Surgery of Shanghai Ninth People's Hospital, Shanghai Jiaotong University School of Medicine, who has made great efforts in the compilation of this book during his study in Kleinert Kutz Hand Surgery Center. Thanks also go to Di Jing, associate professor of Anatomy Teaching and Research Office of China Medical University for the charting in relevant chapters.

Jinghong Xu

July 2014

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1 Embryonic Auxanology, Etiology, and Pathology of Congenital Deformities of the Hands and Upper Limbs

Jinghong Xu, Jialiang Chen, Wei Wang, Bin Wang, Yijia Yu, Bo Chen, and Jianmin Yao

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1.1 Embryonic Development of the Hands and Upper Limbs

Jinghong Xu, Jialiang Chen, Wei Wang, and Bin Wang

Embryonic development period is a period starting from fertilization of eggs to the formation of main structure of the body, as for human beings, the 8 weeks from postfertilization to embryogenesis. The development period of limbs is basically the same as that of other human organs, and its duration is from the fourth to eighth week of embryogenesis.

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1.1.1 Formation and Differentiation of the Body Axis

Limb development is a three-dimensional process that occurs in the proximal-distal axis, front-rear axis, and dorsal-ventral axis. During the early period of embryonic development, homeobox (HOX) transcription factor mediates the skull-tail axis to start the differentiation of somites [1–3]. Around the fourth week, the upper limb germinal area is established; the expressions of T-box (TBX5), wingless-type MMTV (WNT), and fibroblast growth factor (FGF) are launched; and the body begins to grow, and the upper limb bud covered with the surface layer of dermal layer bulges from lateral plate mesoderm. The failure of limb bud induction (tetra-amelia syndrome, limb absence) is correlated with WNT3 and FGF10 mutations [4–8]. TBX4 and TBX5 are correlated with development of lower limbs and upper limbs, respectively. TBX5 mutation (Holt-Oram syndrome, hand-heart malformation syndrome) will lead to a series of upper limb deformities. With the formation of the limb bud, its development is along the three axis directions: proximal-distal axis, front-rear (radius-ulna) axis, and the dorsal-ventral axis (Fig. 1.1).

1.1.1.1 Proximal-Distal Axis

The development and differentiation of each axis is controlled by a cluster of cells, which send development message to local tissues and cells that are called "signal center." The FGF10 in mesoblast is connected with radical fringe gene (RFNG) in ectoderm at the apex of the dorsal-ventral border, which enables ectoderm to get thickened to form a signal center of proximal-distal axis which is called "apical ectodermal ridge (AER)" [9–12]. AER can produce WNT3 and some FGFs (FGF4, FGF8, FGF9, and FGF17) to maintain the expression of FGF10 in mesoblast. The FGF10 may promote the cell proliferation in sub-AER areas, and these areas are called progress zones. The mesoderm cells are regulated by the signal center to determine the final differentiation of limb bud. The interaction between FGF and WNT of ectoderm and mesoderm maintains the growth and development of the proximal-distal axis. In humans, there are four HOX gene clusters, labeled as A, B, C, and D, respectively; in rodents, similar genes are replaced by lowercase letters (hoxa 11). For the developing limbs, HOX gene family is expressed sequentially in a complex overlapping manner, that is, expression from near to far in the natural order. Expression of HOX9 starts when the humerus appears, and HOX11 expression is in the forearm region, HOX12 expression in the wrist area, and HOX13 expression in hand. In mice, hoxa 11 or hoxd 11 gene knockout has no significant impact on the development of limbs, and in this way, some excessive structures exist in the gene system; however, hoxa 11 or hoxd 11 gene knockout in a mouse strain will cause the absence of the radius and ulna. The cascade expression of

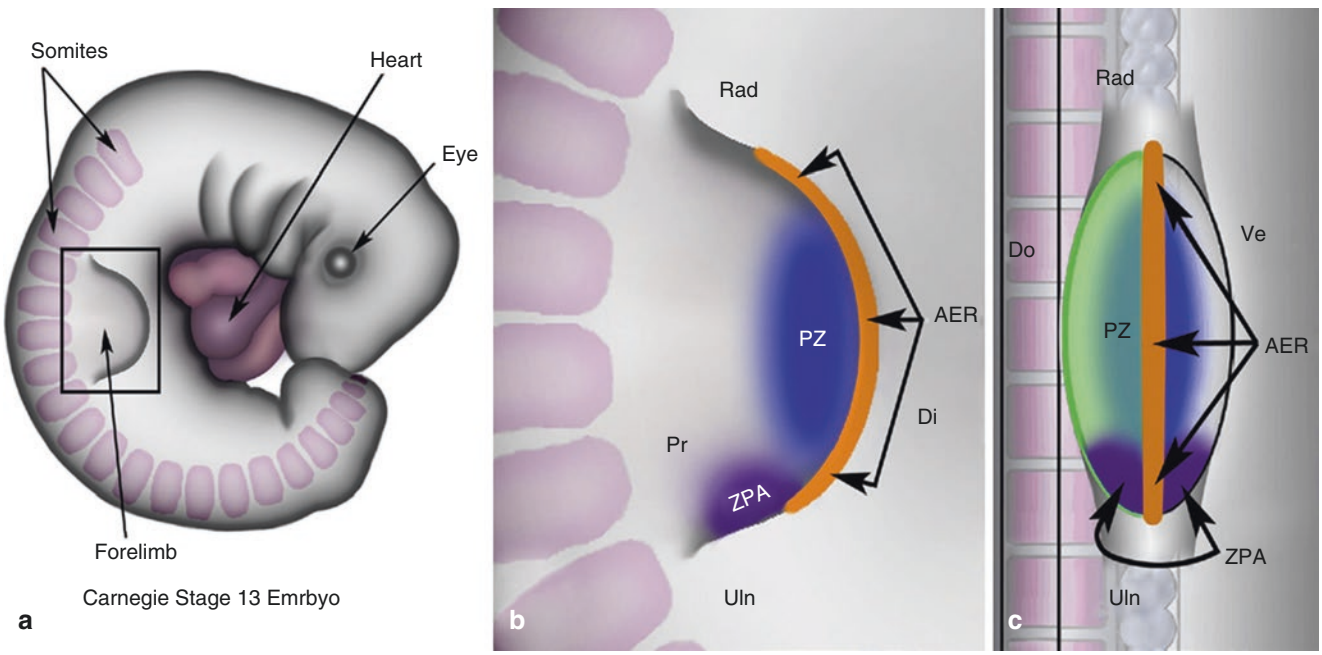

Fig. 1.1 Limb bud regulation center and body axis (Originate from Sekine K, Ohuchi H, Fujiwara M, Yamasaki M, Yoshizawa T, Sato T, et al. Fgf10 is essential for limb and lung formation. Nat Genet 1999;21:138–141) (Reprint with permission from NATURE PUBLISHING GROUP LICENSE TERMS AND CONDITIONS)

HOX gene is partially regulated by FGF secreted by the apex ectodermal ridge and also affected by sonic hedgehog (SHH) signal path [13, 14].

1.1.1.2 Front-Rear Axis

Studies have shown that the development position of hand plate will change from front axis to rear axis when a small area of the rear axis of limb buds is transplanted to the front axis, so that mirror hand is formed. Under the influence of the rear-axis tissue polarization, the front axis of limb bud becomes rear-axis zone of polarizing activity (ZPA). The development and differentiation of the front-rear (radial-ulnar) axis is controlled by the ZPA behind the mesoderm. ZPA can increase the width of the limbs, making it develop backward (ulna). One of the early active factors in ZPA is possibly the vitamin A acid, because the transplantation of vitamin A acid can replicate the effect of ZPA transplantation; however, subsequent studies have shown that vitamin A acid cannot play a biological role in the normal development of limb. ZPA activity is achieved by morphogen SHH [15]. AER is closely linked with ZPA through a feedback loop to maintain the expression of SHH in the rear (ulna) border of distal AER in the growth progress (Fig. 1.2).

1.1.1.3 Dorsal-Ventral Axis

Early limb bud is clearly divided into two parts: dorsal part and ventral part. There is no cell that crosses dorsal and ventral border during development process. The ectoderm covering the limb bud has a certain influence on the interface of dorsal-ventral axis, because cutting and separating of the ectoderm and the dorsal-ventral transposition will lead to reversion of dorsal and ventral parts during limb bud development. Engrailed 1 (En1) protein expression is strictly confined to the ventral chamber. En1 is controlled by one or more bone morphogenetic proteins (BMP), which produce the biological effects through En1. En1 inhibits the activity of WNT7a in ventral chamber. WNT7a makes the mesoderm of the lower limb grow toward the dorsal side by inducing Lim homeobox isogenous transcription factor LMX1B; therefore, the WNT7a deficiency will cause the growth and development disorder of the limbs at the ulnar side. It also suggests another important role of WNT7a of maintaining the production of SHH associated with ZPA [16, 17].

Signal center is also able to regulate the generation of downstream target tissues such as bone, blood vessels, muscles, and nerves through conventional and special, asymmetrical molecular pathways. For example, the generation of bones requires several factors to play regulatory roles at the right time and location, including high mobility group protein9 (SOX9) associated with the Y in sex-determining region, which makes the bone primordial concentrate. WNTs and growth differentiation factor5 (GDF5) regulate the development of joint; parathyroid hormone (PTHLH), Indian hedgehog (IHH), insulin-like growth factor (IGF), bone morphogenetic proteins (BMP), WNTs, FGF, and osteoblast-specific transcription factor2 (RUNX2) will promote the growth of bone primordial and the subsequent endochondral ossification. In addition, short homeobox gene2 (SHOX2) gets upregulated in the cartilaginous membrane of proximal side, promoting the extension of the humerus; at the same time, the forearm cartilaginous membrane induces SHOX to regulate the growth of radius and ulna. Therefore, the correct induction of downstream path is essential to the full differentiation in each axial direction.

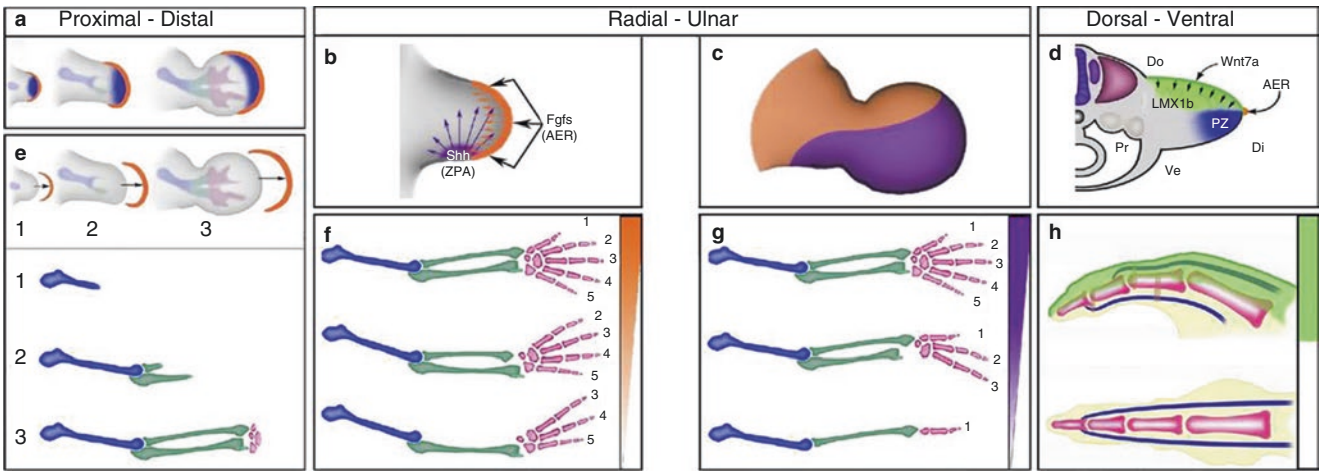

Fig. 1.2 Axial differentiation and developmental disorder (Originate from Saunders JW. The proximo-distal sequence of origin of the parts of the chick wing and the role of ectoderm. J Exp Zool 1948: 108: 363–403) (Reprint with permission from JOHN WILEY AND SONS LICENSE TERMS AND CONDITIONS)

1.1.2 Limb Bud Formation

At 26 days of development, segment, corresponding to the first cervical vertebra at 5–8, a mesodermal ridge appears at the ventrolateral wall of both embryonic sides and near the root of the neck segment, and it is covered with the ectoderm. This is just the upper limb buds, which is the famous Wolff top (Fig. 1.3); at 28 days, upper limb buds are clearly visible (Fig. 1.4).

The limb bud consists of mesoblastic mesenchymal tissues and one ectodermic layer on their surface. In the early stage when the limb bud appears, the apical ectodermal ridge is formed by the ectoderm at the top of limb buds. Many studies have shown that apical ectodermal ridge directly influences and controls the development and differentiation of limbs. Some earliest limb deformities are caused by incomplete differentiation or injuries of apical ectodermal ridge.

At 28–30 days of development, the upper limb bud becomes thickened and bends toward the body side (Fig. 1.6); At 31–32 days, the cylindrical proximal portion and the flat distal portion can be distinguished in upper limb buds, the latter of which is called hand plate; at 33 days, the upper arm, forearm, and hand plate can be distinguished in upper limb buds, and even the segmented structure of hand, i.e., wrist, hand, and finger plate, can be respectively seen, but no finger-dividing sign is seen (Fig. 1.7).

At 35 days of development, finger-dividing signs appear on the hand plate of upper limb buds, and muscles and bone tissue are visible in the limb buds in mesodermal tissues, but at this stage it is unable to distinguish between the bones and muscle tissues (Fig. 1.8). At 37 days of development, the upper limb bud development goes through the fin shape and the slurry shape, and then the fingers with traces are formed with webbed appearance, which are called webbed fingers, and elbows emerge (Fig. 1.9).

1.1.3 Limb Development

Limb develops in the order from the proximal end to the distal end. At 5–8 weeks of development, the generation of upper limbs of each segment is shown in Fig. 1.5.

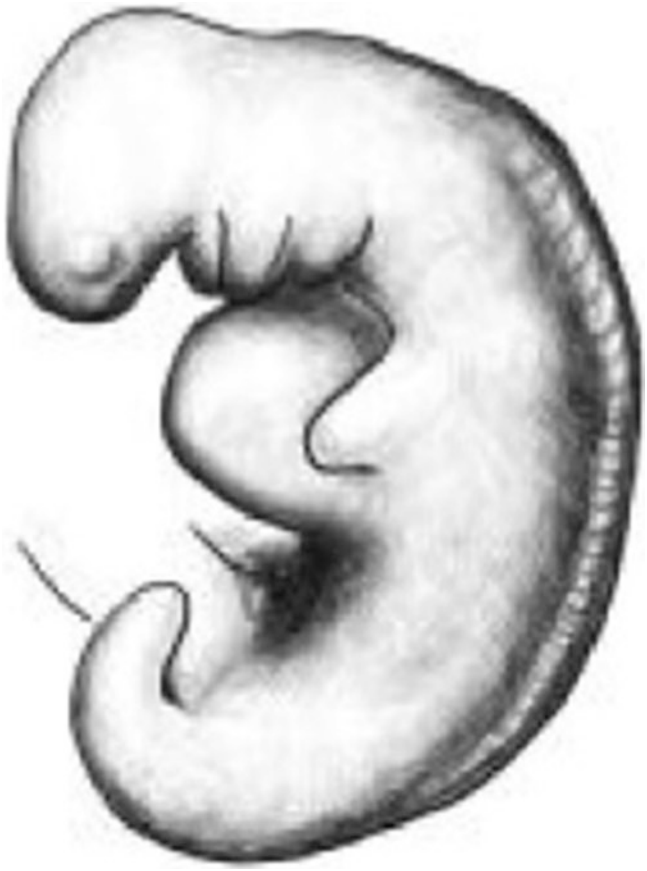

Fig. 1.3 At 26 days of development, with a length of 3.5 mm, the trace of upper limb bud appears at ventral side

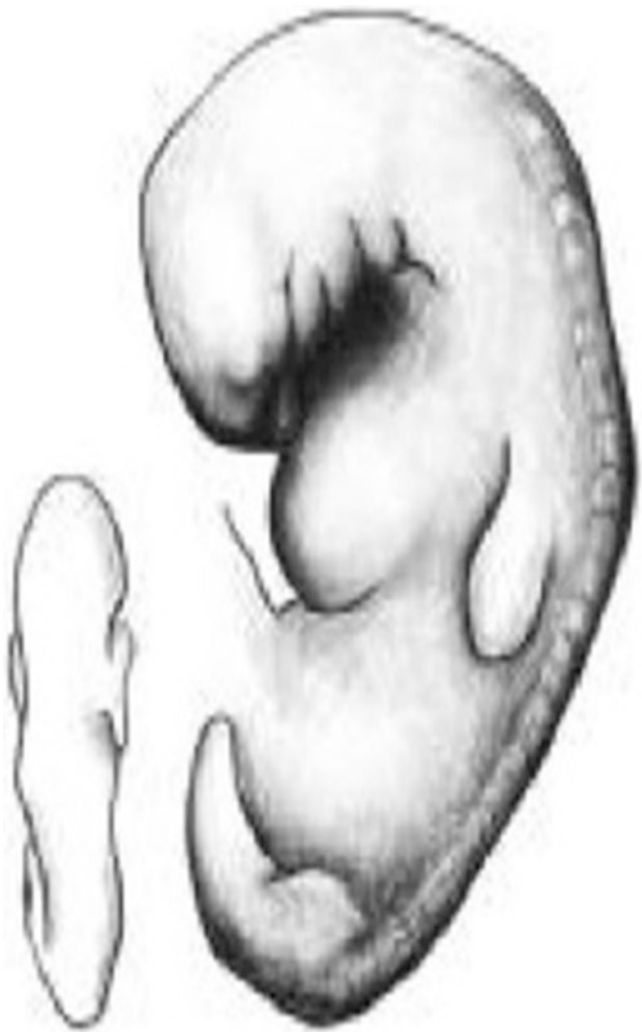

Fig. 1.4 At 28 days of development, with a length of 4–5 mm, upper limb buds are clearly visible

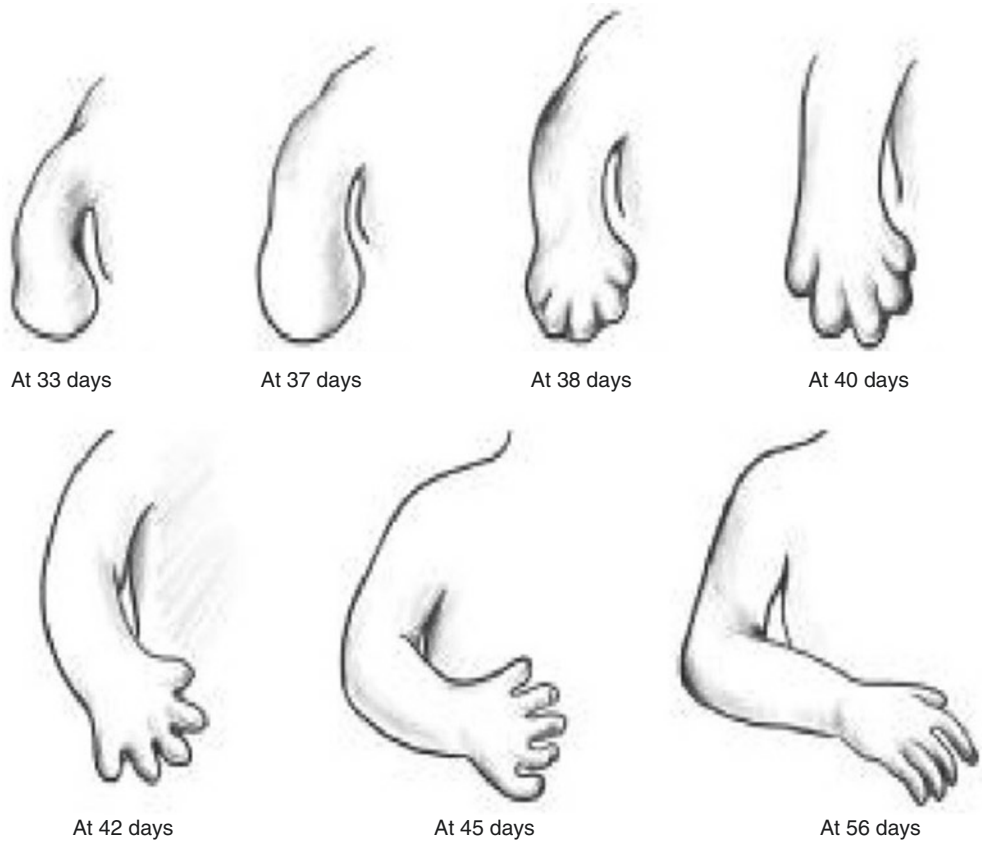

Fig. 1.5 At 5–8 weeks of development, the segments of upper limb develop smoothly

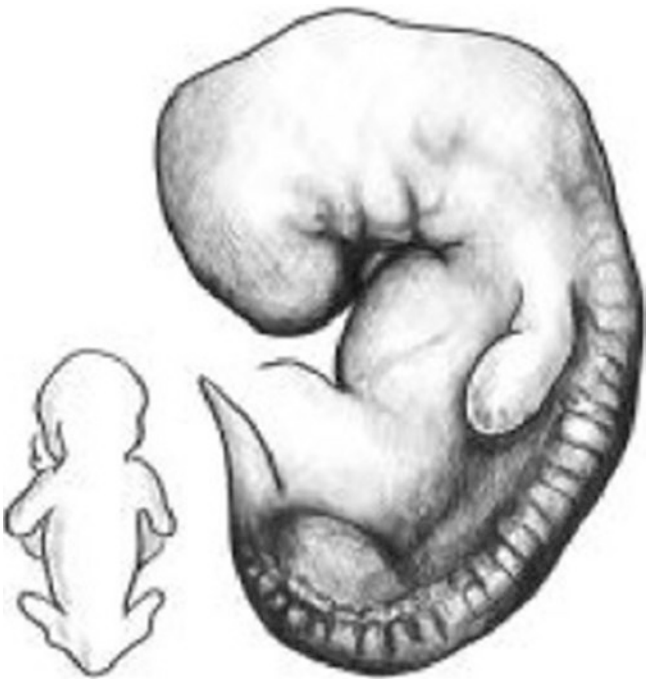

Fig. 1.6 At 28–30 days of development, with a length of 6 ~ 7 mm, upper limb bud already has segmentation

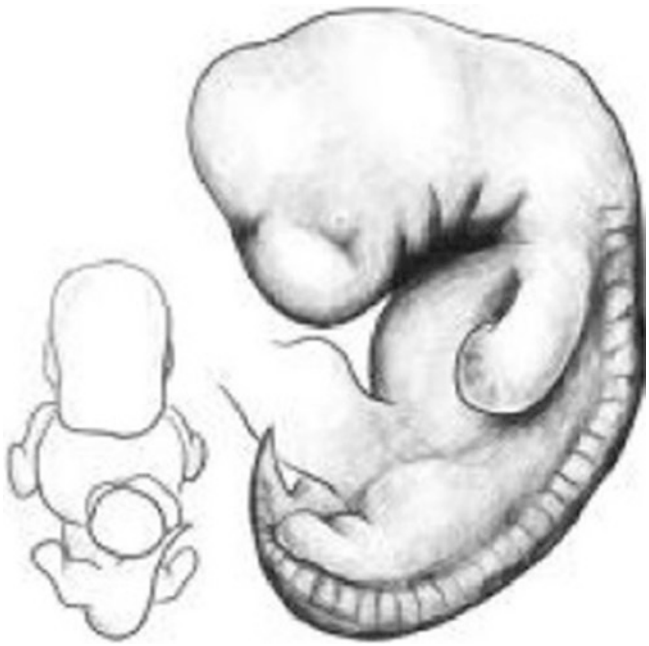

Fig. 1.7 At 33 days of development, with a length of 8 ~ 11 mm, upper arm, forearm, and hand plate can be distinguished in upper limb buds, and lower limb buds are also segmented structurally

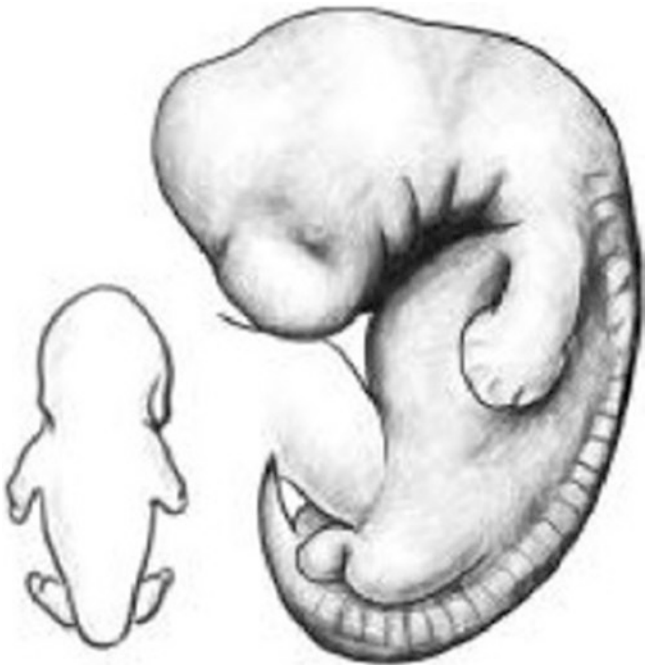

Fig. 1.8 At 35 days of development, with a length of 11–14 mm, finger-dividing signs appear on the hand plate of upper limb buds

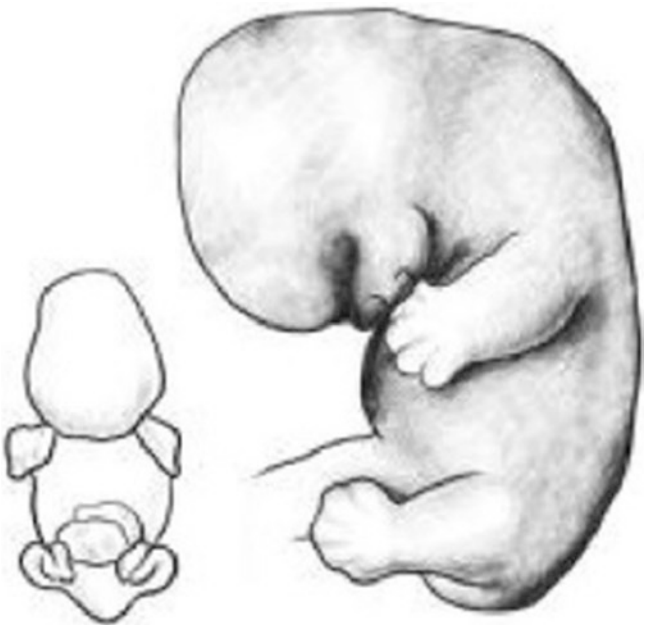

Fig. 1.10 At 39 days of development, with a length of 17–20 mm, palms face each other

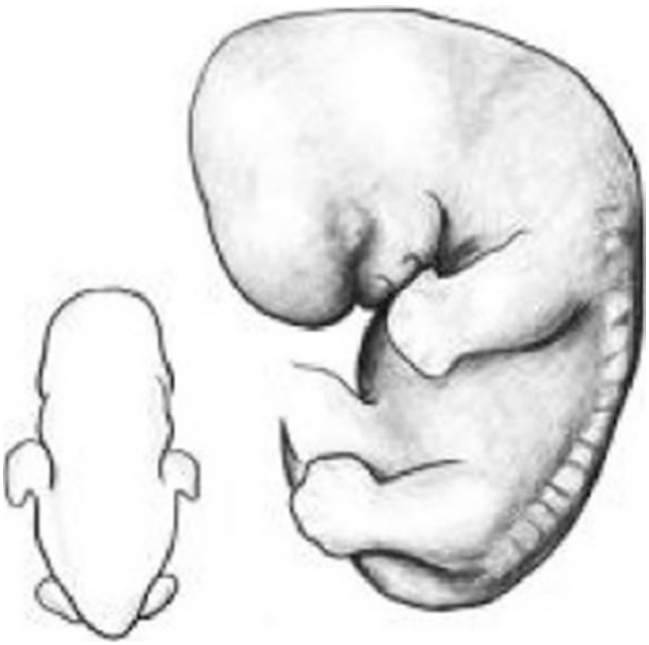

Fig. 1.9 At 37 days of development, the hand plate of upper limb bud has clearly divided fingers, which are webbed

Fig. 1.11 At 40–45 days of development, with a length of 21–23 mm, the fingers have divided completely

At 39 days of development, the palms face each other (Fig. 1.10); at 40–45 days, the finger begins to differentiate, and it becomes bigger and takes shape. At this time the nerves come into the mesenchymal tissues of limb buds from the spinal cord, and muscle composition is clearly visible. And the rest of mesenchymal tissues evolve into the original shape of cartilage and then become ossified to the bones (Fig. 1.11); at 56 days, upper limb takes shape (Fig. 1.12).

Fig. 1.12 At 56 days of development, with a length of 25–27 mm, upper and lower limbs have taken shape

With the increase in limb length, bones are gradually formed, and the myoblasts gather and then differentiate into limb muscle group. These muscle groups are divided into extensor group at dorsal part and flexor group at ventral part. At 7 weeks of development, most of the limb structures have been formed, and joints emerge. Muscles and unique individual muscles can be differentiated. The limbs rotate from the original ventral direction to the opposite direction. Initially, its flexor surface turns toward the ventral side, and then the extensor surface turns toward the dorsal side. Whether it is the upper or lower limb bud, there is a difference between cephalic side and caudal side. The former refers to the side next to the embryonic head, which is located in the anterior edge of the long axis of the limbs, called axis anterior edge; the latter refers to the side close to the rear embryonic side, which is located in the posterior edge of the long axis of the limbs, called axis posterior edge. Axis anterior edge is facing the head, while the axis posterior edge is facing the end (Fig. 1.13).

1.1.4 Skeletal Development

In the early stage of limb morphogenesis, the mesenchyme of the limb bud becomes dense. At around 6 weeks of development, chondrocytes appear and are embedded in a matrix of basophils, gradually showing the characteristics of hyaline cartilage, and further generating bone tissues in the way of entochondrostosis.

Limb bones include shoulder girdle, pelvic girdle, and free bones of upper and lower limbs. The time when ossification centers appear and the corresponding number vary. Clavicle bone is the first bone that experiences ossification, which appears at 7 weeks of development and contains two ossification centers. Entochondrostosis occurs at both ends,

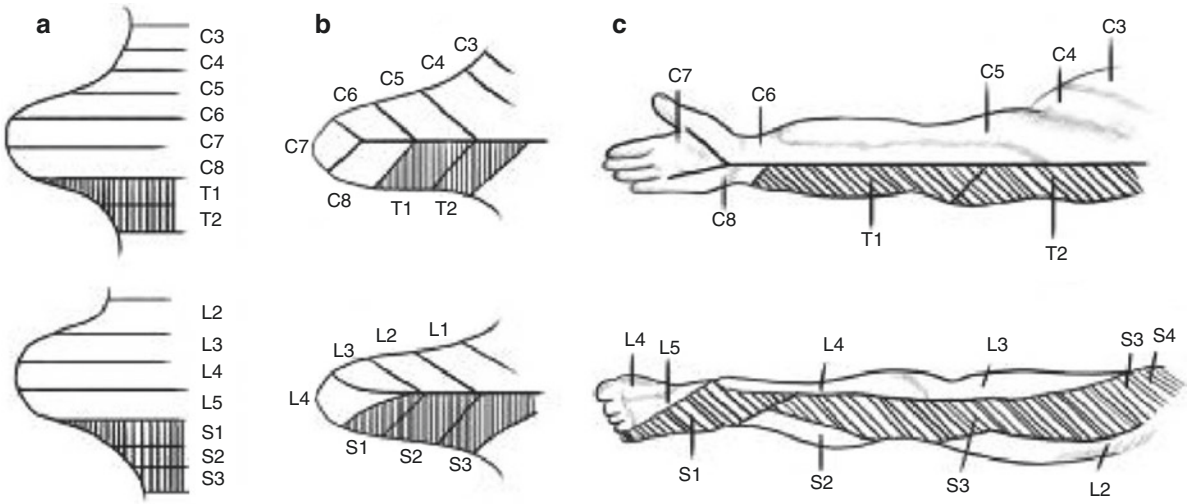

Fig. 1.13 Relationship between distribution of adult upper and lower limb cutaneous nerves and neural development process of embryonic stage

while intramembranous ossification occurs in the middle. The shoulder peak and the mesoscapula of the shoulder girdle bone have an ossification center, and there is an ossification center at the coracoid. Iliac ossification center of pelvic girdle bone appears earlier than pubis and ischium, but it is not completely ossified until adolescence, and when people are 14–16 years old, they become mutually healed to become hip bone.

The upper limb ossification centers appear in such order: the humeri (8) → radii (3) → ulnae (3) → distal knuckle bones (2) → metacarpi (2) → proximal knuckle bones (2) → middle knuckle bones (2) → carpale (1). Generally, if a comparison is made in terms of the growth rate of fetal long bones of four limbs, the growth rate of the forearm bone is the same as that of focile, but the growth rate of the distal segment is slightly faster than that of the proximal segment; the growth rate of lower segment of lower limbs is faster than that of the corresponding segment of the upper limb. Women's ossification centers appear earlier than men's.

1.1.5 Muscular Development

According to embryology and tracing observation of adult innervation, it is generally considered that limb muscles are formed by the myotome of neck and lumbar region extending into the ventral limb bud; however, the source of limb muscles' somites cannot be traced for mammalian embryos, so most scholars now believe that mammalian limb muscle does not originate from the somites. With the elongation of limb bud and formation of limb bud bone, at 7 weeks of development, the myoblasts evolving from the corresponding section of mesoblastic mesenchymal cell layer become aggregated locally and become differentiated to myoblasts, which are gradually transformed into muscle cells. With the bone as the vertical axis, it can be divided into postaxial muscles at the back of limbs (extensor group) and preaxial muscle at the ventral surface of the limbs (flexor group). The upper limb muscles appear a little earlier than the lower limb muscles, the proximal muscles of limbs appear earlier than the distal muscles, and the extensors appear earlier than the flexors. At the beginning of the seventh embryonic week, limbs become extended to the ventral side until the late stage of development, and the upper limbs rotate outward by 90° along their long axis, causing the future elbow to protrude toward the dorsal side and the extensor group toward the dorsal-lateral side. The lower limbs rotate by nearly 90° toward the interiors of their long axis, making the future knee protrude forward, that is, the ventrolateral side, the extensor group turning to the ventral side and the flexor group turning to the dorsal side. Usually at the 8 weeks of development, the main muscles of the limbs nearly take shape.

1.1.6 Vascular Development

Limb arteries originate from intersegmental artery of the corresponding body segments of limb buds; the lateral branch of intersegmental arteries constitute vascular plexus and grow along the long axis of the limbs to form the limb axial artery and its branches. Sources of the upper limb arteries on both sides are slightly different. The left side originates from the left artery in section 7, and the right side originates from the right artery in section 7 and the fourth arterial arch. Subclavian artery is formed by artery axis, and it extends downward into the upper limbs, becomes close to the descending median nerve, and reaches the front of the forearm interosseous membrane. In its advancement, vessels develop into axillary artery, brachial artery, palmar interosseous artery, and deep palmar arterial arch, and ulnar artery and radial artery occur relatively late.

Superficial vein of limb is formed by the edge vein of the upper limb bud. As the fingers of the upper limb bud become differentiated into finger arrangement, the edge vein of the upper limb preaxial margin (i.e., upper limb cephalic vein) is developed into cephalic vein, and the edge vein of the postaxial margin (i.e., upper limb caudal vein) is developed into basilic vein. In adults, the venous location proves the existence of the rotating stage of limbs during embryonic development.

1.1.7 Nerve Development

With the development of embryonic body wall (ectoderm and somatic mesoderm), spinal nerves also enter the limbs. The feeling of adult limb skin is strictly divided according to the source of spinal nerve, i.e., according to dermatomere distribution. The boundary of each dermatomere is determined by the distribution of its corresponding spinal nerves and sympathetic nerves.

The nerves of limbs are from the corresponding nerve plexus. For example, the brachial plexuses entering the upper limbs consist of the anterior branches of spinal nerves from the lower segment of neck and the upper segment of chest. These nerves are re-splitted and recombined during the limb advancement process and make up different nerve trunks and nerve bundles. They are both anatomical unit and functional unit. For example, the medial and lateral cords of the brachial plexus are dominated by dominating flexor groups, and the rear cord is dominated by dominating extensor group. But there are exceptions. For example, the innervation of brachial muscles is both from the musculocutaneous nerves of dominating flexor group and the radial nerves of dominating extensor group.

1.2 Function Development of the Hands and Upper Limbs

Jinghong Xu, Yijia Yu, Bo Chen, and Jianmin Yao

The hands and upper limbs are the main human organs that are engaged in precise operation and daily activities. They not only have motor function and can complete a variety of intricate movements accurately and powerfully but also serve sensing function, particularly physical and sensory functions, which is very important for flexible movement of hands. Maria Montessori (1909) [18], an Italian educator, called our hands "the wise tool" in his book. Application of hand in all aspects including movement, society, language, and cognition starts when life begins. The long-term hand development itself shows the complexity of hand function. Because of this, people call hands the "almighty hand." The hand functional development follows the law of overall development of motion, that is, from top to bottom, from near to far, from generalization to concentration, from positive to negative, and from roughness to precision.

1.2.1 Factors Affecting the Development of Hand and Upper Limb Functions

1.2.1.1 Relationship Between the Nervous System and Hand Functional Development

The evolution of the human cerebral cortex allows hands to possess high flexibility and skill; therefore, hand is the executor and recipient of the brain. Single finger movement depends on the original motor cortex and pyramidal tract and also depends on the sensory feedback reaching the original sensory cortex. For example, touch can adjust grip strength, which is maintained through continuous monitoring; in the integration of sensory information (visual, tactile, and temperature sensation) of complex action (such as tying shoestrings), the posterior cerebral parietal cortex plays an important role [19]. Hand feeling has important effects on sports, that is, it offers various kinds of environmental information, and affects and adjusts hand movement. On the occasion of hand movement, the sensory information continues to be imported to the cerebral cortex, so as to guide and coordinate its motion. The cerebral cortex can integrate information from the tactile neurons, which allows the cooperative work of agonistic muscle and antagonistic muscle to control and coordinate hand movements.

The visual and tactile (sensory and motor) functions of infants are independent from each other within the several months after their birth. However, as they grow, they will coordinate their eyes and hands and become gradually able to fiddle with objects out of their visual range. Sensory nerves and motor nerves of the forearm, wrist, and hand are equally important, which can detect the size, weight, temperature, texture, and other information of objects through touch, pain and temperature sensation, and other body surface receptors, and can transmit stimulation to the brain cortex by nerve impulses. The deep receptors at the nerve endings within the muscle and tendon provide proprioception, kinesthesia, and perception of pressure and joint sites [20–22].

1.2.1.2 Relationship Between Movability and Stability and Hand Functional Developmental Development

Paillard (1970) believed that stability of posture is essential to complete grip movement, and this movement can be divided into three major phases: ① eye-head positioning, which determines the correct position of the hand and arm; ② torso stability, which ensures effective upper limb movement; and ③ control over motion and stability of each joint of hands and arms, to complete precise grip. This order is consistent with the order of normal development [23–26].

1.2.1.3 Relationship Between Anatomic Structure and Hand Functional Development

The arrangement of 27 metacarpal bones and phalanges of human body forms an internal structural basis for hand function. The good combination of bone and supporting soft tissue, such as ligaments, tendons, and muscles, provides stability and mobility for various activities of hands including all joints. Throughout the entire childhood stage, the hand functional development continuously changes proportionally in the same way of the changes in the size of the hand. Hand functional development process of children aged 6–11 shows that the size of hands is correlated with changes in physical strength, which enables surgeons to predict the effects of hand surgery on children in a development phase through the height, age, sex, dominant hand, or other parameters of children [27–32].

1.2.1.4 Relationship Between Environment and Hand Functional Development

Various functional activities of hand require relatively stable external environment or body position. The relatively stable shoulder, elbow, and wrist joints can help effectively control and adjust the direction of motion and strength of the hand, and five-finger separation movements dominated by palm bow and the intrinsic muscles also depend on the stability of wrist joint. Gravity plays a key role in the final development

and improvement of the body, and mechanical stimulation generated by gravity is necessary to bone growth and establishment of the integrity of soft tissues surrounding the joint [30, 31].

1.2.2 The Development Process of the Hands and Upper Limbs

Hand functional development includes the whole process, from unconscious reflex activity to conscious posture maintaining and precision movement, such as initial perception and use of tools, development of dominant hand, and development of object gripping capabilities [18, 32].

1.2.2.1 Development of Grip Ability

Grip is the primary and most fundamental precision movement of individuals. Continuous development of grip ability enables human to make complex, smart, and accurate movements and enables hands to use tools.

At the age of around 3 months, with the disappearance of grasp reflex, a baby begins to unconsciously grip objects, which marks the beginning of its hand functional development. At the age of around 6 months, a baby begins to casually grip objects. During this process, its hand-eye coordination gradually develops. When gripping an object, it often first uses the ulnar side of the palm and then the entire palm. As it is growing, it gradually uses its radial side to grip an object or even nips up an object with its fingers (Figs. 1.14, 1.15, and 1.16) [33].

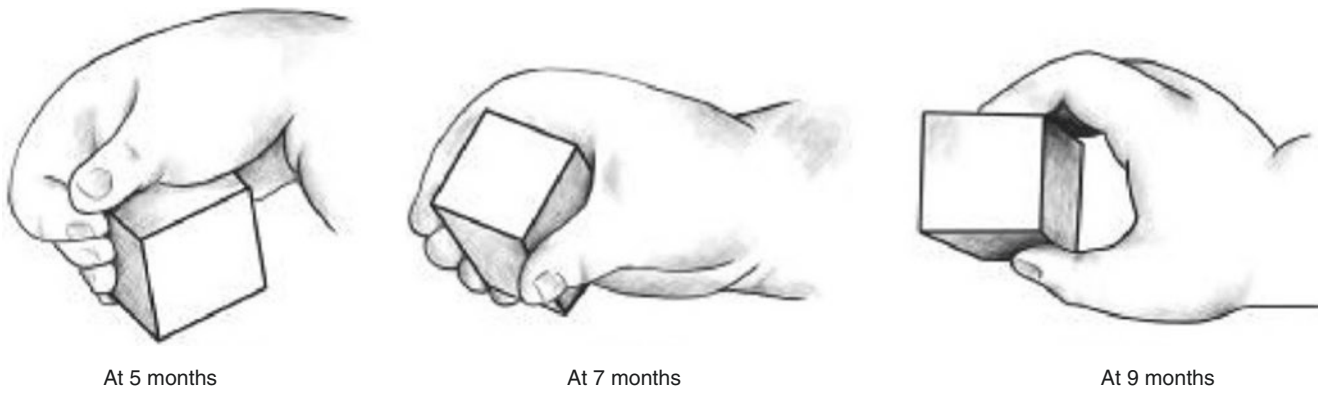

Fig. 1.14 Development process of grip function

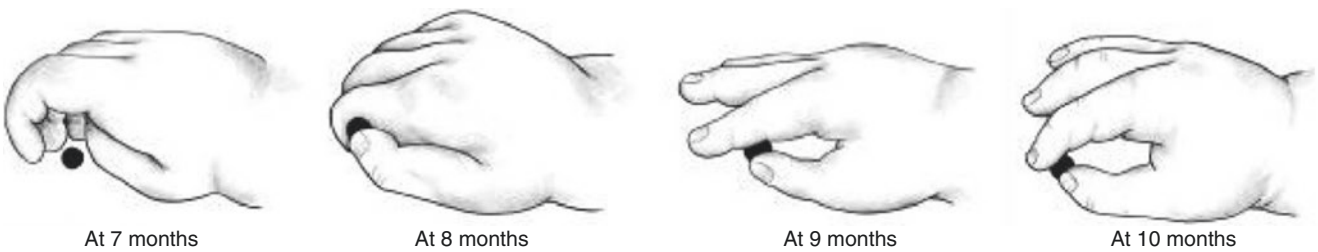

Fig. 1.15 Development process of pellet gripping action

Fig. 1.16 Development process of cylindrical object gripping action (Redrawn from Stephen J. Mathes. MD. plastic surgery second edition, 2007., volume 8, the hand and upper limb, part 2:43)

1.2.2.2 Tools Can Guide and Promote the Hand Functional Development

The morphological characteristics of tools used for eating for a baby can affect the function and efficiency of food intake. For example, the use of spoon with a recess handle enables a baby to more easily grasp it and get food. People usually experience a tool-using process from clumsy grip to precise and delicate pinch and holding; the contact with the object often shifts from the proximal end to the distal end, and the process is that flexion of wrist joint is gradually developed into dorsiflexion.

Pencil-pinching action for children aged 1–6 has shown organic combination of stability and movement (Fig. 1.17). Neuromuscular development proceeds from proximal part to distal part. Take writing and painting, for example. The shoulder joint first moves, and then the elbow joint, and then the wrist joint, and finally the metacarpophalangeal joint. Large joints at the proximal side maintain stability, while the more distant joint shows flexibility. All actions follow a similar pattern: every successful action depends on the stability and proper movement of the upper limbs. The palmar supinated grip requires the coordination of shoulder joint motion, while the pronated grip requires the coordination of elbow and forearm movement and even requires the shoulder joint to remain stable; static tripod grip is often accompanied by the movement beyond from the wrist joint, while mature dynamic tripod grip requires relatively fixed shoulder joint, elbow joint, wrist joint, metacarpophalangeal joint, etc., so that fingers can make subtle and precise movements of flexion and extension.

1.2.2.3 Development of Dominant Hands

Children under 3 show no obvious dominant hand. One does not develop obviously dominant hand until he/she becomes 8–9 years old. Researches reveal that infants under the age of 1 year often go through many stages of hand development before they can use one hand and both hands to perform one action more skillfully. According to the demand of functional development, children need to develop one dominant hand. The hands are used to different extents according to the actual need. For example, when pushing a heavy cart, one needs to exert one's strength and hence use both hands equally; when peeling bananas, one uses both hands but mainly uses one of them; when tying shoes, one uses both hands alternately. Work division of both hands and development of dominant hand are of vital importance to the hand functional developments, especially to the performance of complex actions [31].

1.2.2.4 Development of In-Hand Manipulation Capabilities

Napier (1967) observed and analyzed the static grip of hand and classified hand grip into two types: power grip and precision grip [34]. According to Exner (1992), in-hand manipulation refers to a process when a single hand is utilized to adjust the object inside it before grip is loosened so that the object can be in a more effective position [33]. For example, when grasping several coins, one moves them to the fingertips within the hand and then drops them into a vending machine; when writing, one clenches one end of the pen with the thumb and other fingers. Organic integration of stability and movement is the key to in-hand manipulation. When one is doing up a button, doing up a zip, tying up shoelaces, using scissors, or performing a more complex finger action, usually his/her fingers at the ulnar side play the role of stabilizing the object in the hand. A child at the age of around 2 years has basically fully developed his/her grip function of hands and gradually developed his/her in-hand manipulation capabilities. Of course, the in-hand manipulation capabilities need to be improved with the joint use of both hands.

1.2.3 Law of Hand Functional Developments

In the process of a baby's hand development, the ulnar side first develops, and then the radial side, and then the fingers.

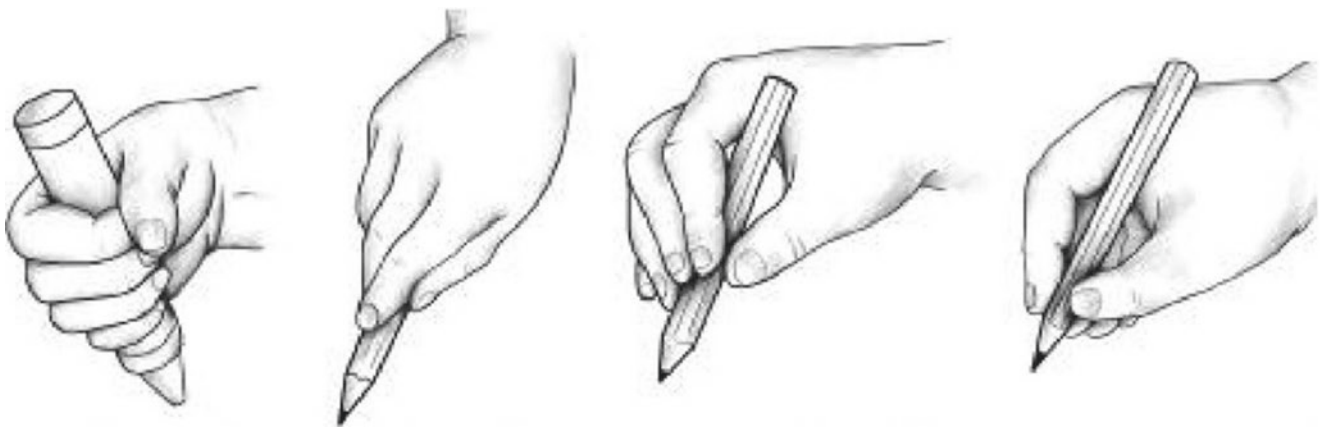

Fig. 1.17 Development process of pencil gripping from near to far

During the early development of hand, a baby gets an object by pressing its four fingers against the center of its palm. With the development of its hand, it tries to grab an object with its thumb and index finger. At an early age, a baby grabs an object without letting it go. It can only lose hold of an object when getting older. Generally, a baby begins to unconsciously touch something at the age of 3 months and becomes able to grab something consciously at the age of 5 months. The baby does not use all its five fingers to cooperatively do different parts of work until it turns 6 months [33, 35].

The process of hand functional developments is described briefly as follows [30]:

1. Neonate. The infant reflectively clenches its fist due to grasping reflex. The thumbs are often adducted and it clenches its fist more tightly when forced to be opened.
2. Month 2. The two hands are opened occasionally, and the time of opening becomes lengthened gradually.
3. Month 3. The two hands are completely opened, and the infant can grasp the object and put it onto the hands; the infant occasionally drag sits own clothes with difficulty.
4. Month 4. The infant stares at the hands, which can be put together; the infant starts the development of centric position direction (the two hands can be reached to the middle of the body) and uses hands or mouth to touch objects, and the infant can also put hands into the mouth.
5. Month 5. The infant can put any object in its hand into the mouth and can use two hands to do various actions; the infant begins to make conscious grasping action with the ulnar side (the little finger side). When lying in the supine position, the infant will stretch out the hands to touch the above toys.
6. Month 6. It is a transitional stage of infantile hand functional development. The infant can reach for a toy, can grip the toy with the entire hands, can knock the toy on the desk, can pat its image in the mirror, and can pass the toy from one hand to another.
7. Month 7. The infant starts to grip objects with radial side (the thumb side), can grip the objects with three fingers, i.e., thumb, index finger, and middle finger, and can pick up fallen objects.
8. Month 8. The infant still grasps objects with the radial side and can pick a raisin-sized object through thumb and index finger and with the remaining three fingers in extension position; the infant can occasionally use two hands to firmly grip a toy.
9. Month 9. The infant can use the ventral side of the last segment of the thumb and index finger to pinch an object and freely let go of the object gripped in the hand and can use two hands or one hand to grip an object; the hands can cross the body midline, that is, stretch out diagonally.
10. Month 10. The two hands coordinates, and the infant can use two hands to grasp one object each and knock it; when supporting the body with its forearm on a desk, it can nip objects by pressing the thumb against the index finger.
11. Month 11. The infant can use the tips of thumb and index finger to pinch objects, but the hand still needs to be left on the desk as the infant cannot pick the object up.
12. Month 12. The infant can pinch an object with thumb and index finger like pinching an object with a forceps; after pinching, the hands can be elevated and leave the desk.
13. Month 15. The infant can put a small object into a cup or bottle and can also pour the object from the cup or the bottle.
14. Month 18. The infant can build 2–3 layers of toy bricks and can pour the water in one cup into another cup.
15. Month 21. The infant can build 4–6 layers of toy bricks and can scribble on the paper with a pencil.
16. At the age of 2 years. The infant can arrange the 2–3 toy bricks in a horizontal line, can screw open the screwed bottle cap and remove it, can turn the pages one by one, and can pass the string through the small holes of beads.
17. At the age of 2.5 years. The infant can use scissors to cut paper and cloth.
18. At the age of 3 years. The infant can use the toy bricks to make them into a door or tunnel shape and keep the hands away from the desk when building the toy bricks; the infant can stretch the upper limbs to grasp a ball.
19. At the age of 4 years. The infant can grasp a large ball when the upper limbs are at the status of flexion and can throw the ball outward from the top of the head.
20. At the age of 5 years. The infant can use scissors to cut various objects.
21. At the age of 6 years. The infant can sustain an object with one hand and do things with the other and can throw a ball and pat a ball. At this stage, the infant can hold a pen basically well like an adult.
22. At the age of 7 years. The infant can knock in a nail with hammer and can throw and hit a ball.
23. At the age of 8 years. The infant can use one hand to grasp a ball and skillfully use scissors.

1.2.4 Evaluation Method of Hand Functional Developments

The fine movement age evaluation scale[36, 37] (Table 1.1) can be used to evaluate the fine movement capabilities of infants aged from 4 months to 6 years, and this scale includes 42 examination items with a total score of 72 points. The less the score is, the lower the developmental level of the fine movement is.

Table 1.1 Fine movement age evaluation scale

Age (month)	Item of examination	Score	Evaluation
4	Gently clench one's fist (1 hand)	4	
7	Grasp a dice with an edge length of 2.5 cm with 1 hand	1	
	Grasp a dice with an edge length of 2.5 cm with thumb and other fingers	1	
	Grasp a dice with an edge length of 2.5 cm with 1 hand and pass it to the other hand	1	
10	Correctly pinch a bead with a diameter of 0.6 cm with the thumb and other fingers	3	
12	Pinch 1 bead and put it into a bottle with a diameter of 5 cm	1	
	Stack 2 cubes with an edge length of 3.7 cm	1	
18	Stack 3 cubes with an edge length of 3.7 cm	6	
21	Stack 5 cubes with an edge length of 3.7 cm	3	
24	Stack 6 cubes with an edge length of 3.7 cm	1	
	Use hands to turn pages (turn 4 pages in 6 pages)	1	
	Pass a string through the small hole of a bead with a diameter of 1.2 cm	1	
30	Stack 8 cubes with an edge length of 3.7 cm	3	
	Grip a crayon to write	3	
36	Stack 9 cubes with an edge length of 3.7 cm	3	
	Put a bead into 1 bottle (10 beads, completed within 30 s)	3	
48	Put a bead into 1 bottle (10 beads, completed within 25 s)	3	
	Draw a circle with a pen	3	
	Use a healthy hand to press 3 buttons (9 times completed within 10 s)	1.5	
	Use an affected hand to press 3 buttons (8 times completed within 10 s)	1.5	
	Lift 45 small rods (completed within 180 s)	3	
60	Draw a quadrangle with a pen	6	
	Put a bead into one bottle (10 beads, completed within 20 s)	6	
66	Wind a coil (completed within 30 s)	0.6	
	Lift 45 nails (completed within 140 s)	0.7	
	Lift 5 nails with a forceps (completed within 60 s)	0.7	
	Use a healthy hand to press 3 electric buttons (10 times completed within 10 s)	0.7	
	Use an affected hand to press 3 electric buttons (9 times completed within 10 s)	0.7	
	Press 2 electric buttons at the horizontal level (6 times completed within 10 s)	0.7	
	Press 2 electric buttons at the vertical level (6 times completed within 10 s)	0.7	
	Use a healthy hand to turn the screw (completed within 55 s)	0.6	
	Use an affected hand to turn the screw (completed within 55 s)	0.6	
72	Draw a 5-pointed star with a pen	0.6	
	Wind a coil (completed within 15 s)	0.6	
	Lift 5 nails with a forceps (completed within 35 s)	0.6	
	Lift 45 nails (completed within 130 s)	0.6	
	Use a healthy hand to press 3 electric buttons (11 times completed within 10 s)	0.6	
	Use an affected hand to press 3 electric buttons (10 times completed within 10 s)	0.6	
	Press 2 electric buttons at the horizontal level (8 times completed within 10 s)	0.6	
	Press 2 electric buttons at the vertical level (7 times completed within 10 s)	0.6	
	Use a healthy hand to turn the screw (completed within 50 s)	0.6	
	Use an affected hand to turn the screw (completed within 55 s)	0.6	

1.3 Incidence, Etiology, and Pathogenesis of Congenital Deformities of the Hands and Upper Limbs

Wei Wang and Jianmin Yao

1.3.1 Incidence

Congenital deformities of the hands and upper limbs are a common disease. The Society of Congenital Anomaly of International Federation of Societies for Surgery of the Hand has made a statistical analysis on the report results of seven research centers in the UK, Japan, and the USA in1982 and found that its incidence was 1.1‰. The author et al. (1982) once investigated the birth records of 350,000 neonates in Shanghai urban area. According to them, the incidence of deformities of the hands and upper limbs was 0.85‰. As the neonate birth records in some hospitals were incomplete, the actual incidence might be higher than this figure. A European report indicated that the incidence of the congenital deformities of the limbs was 59.1/10,000 for live newborns. Among all kinds of human congenital deformities, limb deformity accounted for 26%. Lamb (1982) reported that the incidence of congenital deformities of the hands and upper limbs was 1.8‰; as the same neonate might suffer two kinds of deformities of the hands and upper limbs, the actual incidence was 1.09‰. Ivy reported that the incidence of congenital deformities of the upper limbs was as high as 8‰. Woolf et al. reported that the incidence of congenital deformities of the upper limbs was 1/1064 in live newborns in Salt Lake City, USA, from 1951 to 1967.

Congenital deformities of the hands and upper limbs may exist in the form of either one anomaly or multiple deformities, or it can be the manifestation of multiple syndromes. As is reported by Froster (1993), among the 1,213,913 live neonates, a total of 659 suffered from limb defects, 24 of whom were induced by amniotic band. Giele (2001) reported the 11-year incidence of congenital clubhand in Western Australia was 1/506, 46% of the cases were accompanied by other deformities, 51% of the cases were deformities of two hands, and 17% of the cases were multiple hand deformities; the commonest was dysdifferentiation (35%), followed by twin deformity (33%) and dyspoiesis (15%); there was no difference between white and black people.

However, few studies have been done on the incidence of each type of deformity. In 1987, Cheng et al. classified the different kinds of deformity suffered by the 1673 infants with congenital deformities of the hands and upper limbs in eight clinics. Some statistical results obtained by them can be used for reference (Table 1.2).

Flatt A. (1994) [38] recorded the incidence of 2758 cases of various congenital deformities of the hands and upper limbs in his book *Treatment of Congenital Clubhand*, which was of significance (Table 1.3).

Table 1.2 Different kinds of deformity suffered by the 1673 infants with congenital deformities of the hands and upper limbs in eight clinics

Type of deformities	Number of cases (fingers)	Percentage (%)	Range of proportion (%)
Transverse deletion	128	5	0.7–32.5
Longitudinal deletion	410	16	6.6–37.3
Dysplasia	291	11.3	4.3–19.3
Ring constriction	120	4.7	0.9–6.5
Neoplasm	626	24.3	2.4–35.9
Megalomelia and macrodactylia	22	0.9	0.5–2.1
Dysdifferentiation	442	17.1	8.3–26.4
Translocation	166	6.6	2.5–16
Soft tissue deletion	366	14.2	1.2–21.3

Table 1.3 Incidence of various congenital deformities of the hands and upper limbs

Type of deformities	Number of case (fingers)	Percentage (%)
Syndactylia	501	18.2
Polydactylia (total)	403	14.6
Radial polydactylia	184	6.7
Ulnar polydactylia	142	5.1
Central polydactylia	77	2.8
Anomaly of finger flexion	189	6.9
Broken limbs (all)	186	6.7
Broken limbs, broken hands, and broken fingers	80	2.9
Broken limbs, broken arms, and broken forearms	76	2.8
Broken limbs and broken wrists	30	1.1
Anomaly of finger lateral flexion	151	5.5
Anomaly of brachydactylia	143	5.2
Radial clubhand	127	4.6
Central ray deletion (cleft hand)	106	3.8
Dysplasia of thumb	97	3.5
Crossing syndactylia	92	3.3
Snapping finger	63	2.3
Apert's syndrome	62	2.3
Poland's syndrome	60	2.2
Ring constriction	56	2.0
Deletion of muscles and tendons	49	1.8
Deformities of muscles and tendons	45	1.6
Deletion of thumb	39	1.4
Dysplasia of ulnar (bone)	34	1.2
Deletion of ulnar fingers and metacarpal bones	32	1.2
Radial-ulnar bone fusion	30	1.1
Ulnar clubhand	28	1.0
Dysplasia of whole hands	27	1.0
Macrodactyly and megalomelia	26	0.9
Triphalangeal thumb	24	0.9
Phocomelia	19	0.7
Deletion of thumb	19	0.7
Dysplasia of radial (bone)	18	0.6
Phalangeal bone fusion	15	0.5
Others	117	4.2

Congenital deformities of the hands and upper limbs can be accompanied by cardiovascular deformity, hematopoietic system diseases, digestive tract deformity, facial deformity, cranial deformity, genitourinary apparatus deformity, and lower limb deformity.

About 5% of congenital deformities of the hands and upper limbs are one of the manifestations of syndrome. With the development of genetics, people find that the relation between hand deformity and syndrome is as follows: 48 kinds of syndromes show the symptom of aschistodactylia, 36 kinds of syndromes show the symptom of finger lateral flexion, 20 kinds of syndromes show the symptom of finger flexion deformity, and 18 kinds of syndromes show the symptom of brachydactylia. The author finds that the actual figure in clinical practice is bigger than the statistical figure. Take finger flexion deformity for example. Half of the cases are one of the symptoms of different syndromes.

McGuirk (2001) analyzed 161,252 live births and dead births in Boston, USA, from 1972 to 1974 and from 1979 to 1994 and found that the incidence of limb deformity was 0.69‰. The reasons were as follows: ① pure gene mutation, family genetic factors, and known syndrome (24%); ② chromosomal aberration (6%); ③ administration of teratogenic agent (4%); ④ vascular impairment (35%); and ⑤ unknown reasons (31%).

1.3.2 Etiology

The etiologic factors of congenital deformities are very complex, and the exact teratogenic reasons and mechanism are still very unclear at present. The teratogenic reasons can be generally divided into two types: one is intrinsic factor, namely, the genetic factor; the other is external cause, namely, the external factors during the embryonic period.

1.3.2.1 Genetic Factors

The genetic factors include the following: ① chromosomal abnormality, namely, abnormality in chromosome number or structure, and as miscarriage and dead births are induced in most cases, clinical cases are not very common; ② gene mutation, 10–15% of congenital deformities are induced by gene mutation, but most gene mutations will not induce congenital deformities [39–43]. Gene mutations are classified into polygenic mutation and monogenic mutation. The former can result in multiple congenital deformities, and the latter can sometimes result in multiple defects such as acrosphenosyndactylia induced by one single dominant gene.

Gene mutation and congenital deformities are closely associated. P63 gene is one member of the p53 gene family and can be structurally classified into transactivation domain (TAD), DNA binding domain (DBD), oligomerization domain (OD), and SAM structural domain (SAM) (Fig. 1.18). The coding products are multiple isomers with different activities and can be classified into two types: ① the isomers which start transcription from exon 1 and have transactivation domains are called TA isomers; ② the isomers which start transcription from the site between exon 3 and exon 4 and do not have transactivation domain are called Δ*N* isomers; at the same time, due to the differences of 3′ end shearing methods, isomers with the following different C-ends (α, β, and γ) are produced. It has been verified at present that p63 gene plays an important role in the development, differentiation, and morphogenesis of various epithelial tissues, formation of embryo, and development and differentiation of ectoderm. p63 gene is widely expressed in human tissues, such as the esophagus, lungs, skin, muscles, breast glands, spleen, lymphocytes, nervous tissues, digestive system and urogenital system, etc., but its composition in such histiocytes and subcellular localization varies. P63 gene is expressed in AER of limb buds, and the mutation of p63 gene renders the AER unable to complete differentiation, so its structural integrity is maintained. At present, it is found that the mutation of p63 gene is present in ectrodactyly-ectodermal dysplasia-cleft lip/palate syndrome (EEC syndrome), split-hand/split-foot malformation (SHFM), and ankyloblepharon-ectodermal dysplasia-cleft lip/palate syndrome (AEC syndrome). The heterozygous mutation of p63 gene is associated with ectodermal dysplasia, orofacial cleft, and deformity at the limb ends. Till now, 31 mutation sites have been found in patients with EEC syndrome, including five mutational hot spots (R204, R227, R279, R280, and R304), which are located at the DBD of p63 gene and influence the binding of p63 gene and DNA, resulting in the decrease in the transcription activity (Fig. 1.19). The SAM structural domain of p63 gene participates in the interactions between proteins during tissue development and differentiation; therefore, it is speculated that the mutation that occurs to this structure will inhibit the interactions of specific proteins [44–46].

The primary cause of congenital deformities is the inheritance of the genetic factors in cell chromosome to the next generation. Genetic factors play an important role in the occurrence of congenital deformities; according to statistics, about 5% of the hand deformities are genetically induced. Due to blood relationship, among the family members with a family history of deformities, the incidence of deformities is 25 times that of normal population. The majority of hand deformities are induced by monogenic inheritance. The mode of inheritance is autosomal dominant or recessive inheritance and sex-linked inheritance, among which the common type is autosomal dominant inheritance [40, 47, 48]. The genetic regularity is as follows:

The thin arrowhead represents the mutational amino acid residue (K194 and R280) in SHFM, and the thick arrowhead represents the mutational amino acid residue (R279 and R304) in EEC.

1. The morbigenous dominant gene is located at one pair among the 1–22 autosomes. Inheritance is unrelated with

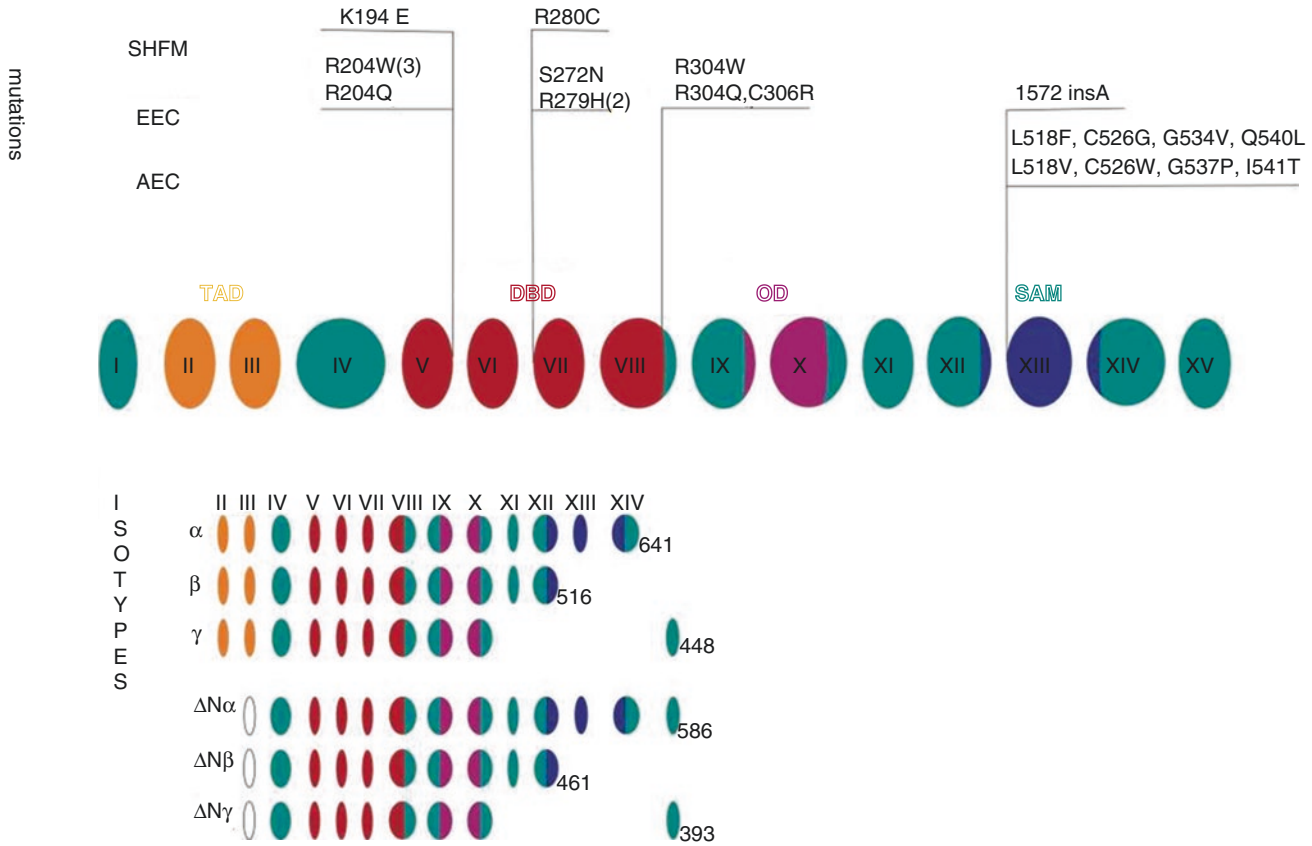

Fig. 1.18 SHFM, EEC, and AEC mutational hot spot of p63 gene (Redrawn from Sifakis S, Basel D, Ianakiev P, Kilpatrick M, Tsipouras P. Clin Genet. Distal limb malformations: underlying mechanisms and clinical associations. 2001;60(3):165–72)

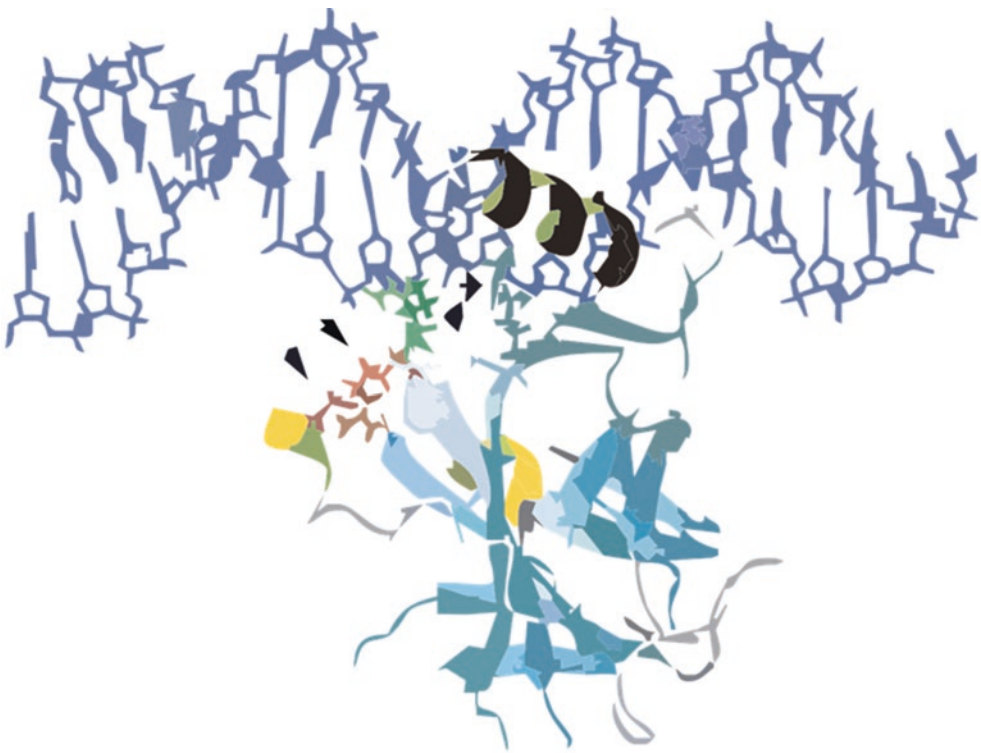

Fig. 1.19 p63 gene DNA binding domain ribbon diagram (Redrawn from Ianakiev P, Kilpatrick MW, Toudjarska I, Basel D, Beighton P, Tsipouras P. Split-hand/split-foot malformation is caused by mutations in the p63 gene on 3q27. AmJ Hum Genet 2000: 67: 59–66) (Reprint with permission from ELSEVIER LICENSE TERMS AND CONDITIONS)

gender, and the pathogenic probability among men and women in the family is the same.
2. Patients can be found in each generation, and the disease may occur commonly within continuous generations in the family.
3. If a patient gets married with a healthy person, the incidence of deformities in their children is 50%; if both are patients, the incidence of deformities in their children is as high as 75%.
4. Different expressivities are present, which means that despite the onset in different individuals with the same genotype, the severity of lesions varies.

The common deformities induced by dominant inheritance include symphalangia, brachydactylia, cleft hand, hyperdactylia, etc. Patients with recessive inheritance usually have no obvious family history. The manifestations of the sex-linked recessive inheritance are men developing the disease and women being the carrier of the pathogenic factor.

Consanguineous marriage is the primary cause of congenital deformities. In case of non-consanguineous marriage, the incidence of deformities in the children is 1‰; in case of consanguineous marriage, the incidence of deformities in the children is 25% to 50%, which is 250 to 500 times as high as that of normal population.

1.3.2.2 External Factors

Under the influence of external factors during the embryonic stage, especially the teratogenic factors in the embryo, hand deformities can also occur. The occurrence of deformities does not involve the genetic factors in chromosomes, so such deformities will not appear in the future generations. The key stage of occurrence of embryonic deformities is the first 3 months after gestation, which might be associated with the following factors:

1. Nutritional factor. Animal experiment studies indicated that, in case of lack of vitamin C in diets for mother mice, the embryonic mice might suffer deformities in flexural limb after birth. Warkany and Nelson fed the white mice with vitamin B_2 deficient feeds. Among the 484 mice born afterward, 189 (39.05%) developed various congenital deformities; half of them developed deformity of forepaw. The deficiency of vitamin A can affect the development of embryonic soft tissues and can induce the deformities in the heart, eyes, diaphragm, and genitourinary apparatus.

   In human kind, there are few cases where the mothers are undernourished, but some placental lesions will affect fetal nutritional supply, further influencing embryonic development and inducing the occurrence of hand deformities.
2. Drug factor. Many drugs have a teratogenic effect, including sedatives such as thalidomide, anticancer drugs, and oral contraceptives. Animal experiments have verified that cortical hormone, trypan blue, mustard nitrogen, etc. can induce limb deformities in animal embryos. Kosenow and Pfeiffer (1960) reported the relation between occurrence of phocomelia anomaly (short upper limbs, and the hand is connected with the shoulder) and administration of thalidomide during the early pregnancy, and the incidence is up to over 20%. Thalidomide once caused thousands of children in Europe to develop deformities of amelia and micromelia from 1957 to 1961, and this event spurred scholars to carry out the studies on the cause and pathology of congenital deformities. In addition, organomercury, insecticides, etc. are also very important teratogenic factors. For the same drug, the differences in its dosage, route of use, absorption, and metabolism will induce different types of deformities.
3. Radioactive factors. Radioactive rays have a decisive influence on embryonic genetic characteristics and can even cause developmental arrest. After X-ray radiation is performed on white mice, water blister, blood blister, and hematomas can be found in the paws of the embryonic mice. Multiple deformities such as lipomeria, adactylia, cleft limbs, hyperdactylia, and syndactylia are formed after birth, and in the meantime, ocular and renal deformities also occur. After the Second World War, a random examination was carried out on 205 children who were exposed to the atomic bomb explosion during the first half stage of embryo and found 28 developed deformities, which accounted for over 13%, indicating that their incidence was much higher than that of the common population.
4. Endocrine factor. Daraiswami injected a small amount of insulin into the shell of eggs whose incubation was traced so that the hatched chickens would develop multiple deformities, but the occurrence of deformities could be prevented if both niacinamide and vitamin B2 were injected into it. Clinically, the incidence of deformities of future generation of diabetes patients is five to seven times higher than that of healthy population.
5. Disease factor. The exposure of mothers to the infection of some pathogens during the first 3 months such as rubella virus, cytomegalovirus, toxoplasm, herpes simplex virus, Asian influenza virus, epidemic parotitis virus, and *Treponema pallidum* can induce fetal deformities. Gregg (1941) found, in case the mothers developed rubella during the first 2 months after gestation, their fetuses could suffer various kinds of congenital deformities, such as cataract, decreased hearing, heart deformities, and dysostosis, and the reason might be that the virus directly influenced embryonic development through placenta. Other scholars hold that the poor maternal health status might be one supplementary factor that causes

the fetuses with a certain genetic factor for anomaly to develop deformities. In addition, maternal diabetes, chronic ethylism, etc. could also induce fetal deformities. Some reports indicated that thalassemia can induce digital arterial embolism, which results in the deformity of congenital dactylolysis.

6. Trauma factor. Some scholars consider that, during the early embryonic stage, the hematomas in the embryo can inhibit the development of some embryonic parts, further resulting in deformities. During the later stage of pregnancy, the fetus grows rapidly, and the amniotic fluid decreases gradually; in the meantime, the abdominal cavity and pelvic cavity are under increasing pressure. Cotwin or uterine deformities, hysteromyoma, etc. would especially cause the fetal limbs to be subject to compression and their movement to be confined so that the fetal limbs will become flexed and deformities will occur. In addition, the fetal constraint by amniotic band or fibrous ring will also result in intrauterine amputated extremities (fingers).
7. Environmental factor. According to Jones (1973), fetal alcohol syndrome is the syndrome of abnormalities in the head, face, four limbs, heart, and external genitals accompanied by generalized scoliosis and listlessness that are found in infants delivered by pregnant women with ethylism. Hundreds of cases have been reported after his definition of such syndrome. Therefore, pregnant women have been warned that moderate drinking during pregnancy is harmful to the fetuses. In addition, pregnant women who smoke will deliver low birthweight infants, and their mean weight can decrease by 150–250 g. As is reported by other articles, smoking could lead to an increase in miscarriage rate and perinatal mortality rate, and the risk of deformity occurrence in the children delivered by smoking pregnant women is two to three times higher than that in the children delivered by nonsmoking pregnant women.

1.3.3 Pathogenesis

At present, the real pathogenesis of congenital deformities of the upper limbs is little known. Regarding this, two views are currently prevailing: one is that the development process is programmed by gene from the beginning; the other is that development is the result of biological, chemical, and physical effects of sequences and is subject to the influence of four-dimensional spacetime. The two viewpoints lead to the theory of genetic determinism and the theory of environmental determinism. However, more materials indicate that the majority of deformities result from the joint effect of the two factors, but the influence of environmental factors is more significant. The author believes that some congenital deformities of the hands and upper limbs are gene programmed from the beginning, such as deformity of camptodactilia, deformity of finger lateral flexion, cleft hand, and some deformities of syndactylia, and the patients often have an obvious family genetic predisposition; in addition, environmental factors can induce gene mutation or change the normal expression of gene, such as radial clubhand, and the gene defect can somewhat induce deformities only under the influence of some environmental factors.

From the children treated by the author, it is known that the family of one patient has obvious medical history of syndactylia inheritance (Fig. 1.20). There are 38 direct relatives in the five generations of ancestors in their family, 21 of whom suffer congenital aschistodactylia with the incidence of 55.3%. In terms of the shape of deformities, the manifestations are syndactylia of middle and ring fingers, most of which were complete syndactylia, fingernail amalgamation, and ungual phalanx fusion. Among them, there were 19 cases of syndactylia of middle and ring fingers of both hands, a proportion of 90.5%, and two cases of syndactylia of middle and ring fingers of one single hand, a proportion of 9.5%. In terms of gender, nine are men and account for 42.9%, while 12 are women and account for 57.1%.

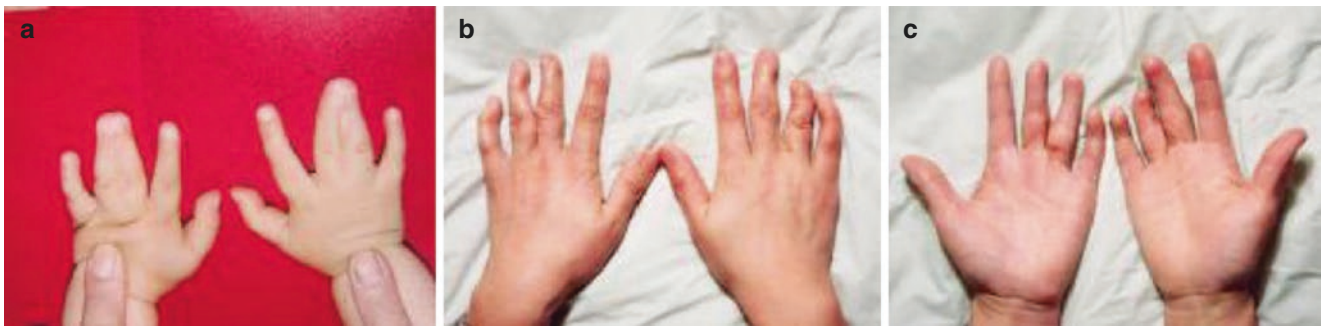

Fig. 1.20 A girl aged 2 years and a half, complete symphalangia of middle and ring fingers, with a family history (**a**). Hand appearance of the patient (**b**). (**c**) Post-surgery for complete syndactylia of both hands of the patient's mother

According to a large quantity of experimental materials, Wilson theoretically classified the mechanism of teratogenic action into nine categories: gene mutation, chromosome aberration, interference with mitochysis, changes in nucleic acid functions and synthesis process, substance insufficiency before the synthesis of protein and enzyme, blocked energy supply, inhibited enzymatic activity, self-stabilization function disorder, and changes in cell membrane characteristics. From the clinical perspective, Beckman and Brent classified the mechanism of action of human teratogenic sources into the following categories: cell death, delayed mitochysis, prolonged cell cycle, delayed differentiation, forced position, insufficient vascular blood supply, histogenesis disorder, and inhibited cell migration.

1.4 Pathology and Genetics of Congenital Deformities of the Hands and Upper Limbs

Jinghong Xu, Jialiang Chen, and Wei Wang

1.4.1 Pathology

The entire process of embryonic development is expressed through gene regulation. The occurrence of all histiocytes is mutually constrained in differentiation and development according to certain genetic information; the primordia of all organs are formed through different mechanisms of histiocyte proliferation, differentiation, local growth, degeneration, and absorption. It should be emphasized that the development zone is a region or a group of cells in embryo and can give a response to the endogenous or the exogenous stimuli as a whole. The defects in the development zone are correlated with the function disorder of primitive cells and the mutual reaction of multiple tissues; for instance, the rostral mesoblastic development disorder can induce head and facial multiple deformities, and the disorder of hypothalamus or vascular tissues can induce deformities in the reproductive organs and heart. During the process of embryonic development, the interference and disorder at any level can induce various kinds of dysplasia and functional disorder, leading to various kinds of congenital deformities and abnormalities, and even embryonic development termination and death. The abnormal phenotypes appearing at all levels of development include:

1. Metabolism disorder: it can be manifested as autosomal recessive or dominant genetic disease.
2. Histogenesis disorder: if two to three embryonic layers and the derivant tissue structures are influenced, the severity is relatively serious; otherwise, the clinical manifestation is relatively mild, and the mode of inheritance can be dominant or recessive.
3. Organ formation disorder: namely, the defects in the structures and functions in organs; various congenital deformities may appear and account for 2–7% of neonate deformities, and 1% of newborns suffer multiple deformities.
4. Deformation disorder: it often occurs in the fetal period 3 months after the conception. The manifestations are obvious changes in the shape and structure of relevant body sites, the majority of which is local involvement. In fetal period, both enzygotic twins and dizygotic twins may suffer deformation due to fetal compression, and such deformations account for 2% of the newborn deformities and can be corrected after birth.

According to the law of embryonic development, different development modes can result in various kinds of deformities, and Patten once proposed six methods: ① hypogrowth, ② hypoabsorption, ③ hyperabsorption, ④ absorption at the wrong sites, ⑤ growth at the abnormal positions, and ⑥ overgrowth of tissues or structures. Arey proposed nine similar methods: ① aplasia, ② hypoplasia, ③ impaired development, ④ adhesion of adjacent primordia, ⑤ overgrowth, ⑥ dislocation, ⑦ incorrect migration, ⑧ atypical, and ⑨ atavism. The modes of occurrence of deformities listed by Cohen (1981) are shown in Table 1.4.

Table 1.4 The congenital deformities induced by abnormalities in embryonic shape

Type	Clinical manifestations
Morphological hypoplasia	
Absence of development	Abrachia, arhinia, renal aplasia, aproctia
Hypoplasia	Achondroplasia, head deformity, and micrognathia deformity
Incompetence	Cleft palate, cheilognathus, and iridocoloboma
Incomplete separation	Ankylodactyly, persistent truncus arteriosus
Incomplete migration	Eversion of cloaca (incomplete orchiocatabasis)
Incomplete rotation	Incomplete intestinal rotation (situs inversus)
Incomplete subsidence	Choanal atresia and Meckel diverticulum
Retention of early positions	Low-set ears and cryptorchidism
Excessive morphogenesia	Polydactylia, dactylomegaly, and big earlobe
Morphogenesia aberration	Struma endothoracica, paradidymal tumor