ABSTRACT

In order to have a better understanding of the classification, it is necessary to clarify the development of ectrodactyly. In order to do so, the authors reviewed papers and analysed their own clinical cases of ectrodactyly and conducted animal experiments to make different models of ectrodactyly. And they found that there should be at least four different types of teratogenic mechanisms of congenital defect of the digits. The first one is longitudinal deficiencies due to mesenchymal cell death in an early developmental stage; the second is abnormal induction of digital rays in the hand plate including cleft hand, central polydactyly and cleft hand. The third is constriction band syndrome, which is caused after digital radiations have been formed, and the fourth is transverse deficiency, in which the critical period is not known.

Key worlds: longitudinal deficiency, radial deficiency, ulnar deficiency, cleft hand, constriction band syndrome, transverse deficiency, symbrachydactyly

INTRODUCTION

Many attempts have been made to classify congenital hand anomalies according to the genetic cause. Swanson’s classification (35) in 1976 was the typical one. Since then, modifications on this classification were made and this classification was adopted by the International Federation of Society for Surgery of the Hand (36). It have been used widely as an IFSSH classification. In this classification, there is no terminology of ectrodactyly and oligodactyly in order to describe congenital absence of digits. The different conditions of congenital absence of digits are classified into different categories as using different diagnostic names instead of ectrodactyly and/or oligodactyly.
This classification is relatively easy to use, but it has its own limitations (22). The biggest one occurs in the classification of ectrodactyly. In order to have a better understanding of the classification, it is necessary to clarify the development of ectrodactyly. In order to do so, the authors analysed clinical cases of ectrodactyly and conducted animal experiments to make different models of ectrodactyly (9, 21, 25, 27, 28).

On the other hand, if something happens during morphogenesis of the upper limb bud or if there is an abnormal gene for formation of the limb, congenital anomalies of the limb may be induced. There are many types of congenital absence of the digits. The teratogenic mechanisms of these deformities were considered to be different, but they are not yet clear. The timing of the insult to the limb bud or hand plate is considered to be one of the most important factors, which influence to induce the different types of congenital absence of the digits, and this timing is called critical period. In authors’ experimental studies, they tried to induce different types of congenital absence of digits by changing the timing of the insults to be added to the embryo. The authors thought that they can classify the congenital absence of digits according to the critical period of each deformity. The authors modified IFSSH classification based on their clinical and experimental studies (29) and it was adopted by the Japanese Society for Surgery of the Hand and is called Japanese modification of the IFSSH classification.

![Fig. 1: Expressions of constriction band syndrome – ① ring constriction, ② ring constriction associated with lymphedema, ③ acrosyndactyly, ④ amputation. (Reprint from Ogino T. Clinical features and teratogenic mechanisms of congenital absence of digits. Dev. Growth Differ. 49: 523-531, 2007.)](image-url)
1. EMBRYOLOGY

In the normal morphogenesis of the upper limb, about 4 weeks after fertilization, the swelling of the limb bud appears and it is covered with ectoderm and contains closely packed mesenchymal cells. Mesenchymal cells were distributed uniformly in the limb bud. One week later, the distal end of the limb bud expands into the hand plate. In the hand plate, mesenchymal cell proliferation occurs in the interdigital areas and the mesenchymal cells migrated to form the digital rays after they proliferated in the interdigital area. During this process, the apical portion of the ectoderm thickens and becomes apical ectodermal ridge (AER). It is believed that the apical ectodermal ridge acts as an inductor of the digital rays. Recent papers reported that definitive forelimb territory is determined by the restricted expression of fibroblast growth factor (FGF) 10 in lateral plate mesoderm. Then FGF10 expression leads to induction of FGF8 expression in the overlying surface ectoderm and initiates limb bud formation. FGF8 in the ectoderm acts on the underlying mesoderm and maintains FGF10 expression. It also induces sonic hedgehog (Shh) expression in the posterior margin of the nascent limb mesoderm. FGF 10 persists in the mesenchyme of the established limb bud and appears to interact with FGF 8 in the apical ectoderm (19, 32). The interaction between FGF 8 and FGF 10 might be a molecular basis for interaction between the AER and the underlying mesoderm. FGF8 maintains the progressive zone mesoderm in an undifferentiated state and contributes to the proximo-distal sequence of the development of the limb.

The radio-ulnar sequence of the development of the limb may be controlled by a zone of polarizing activity (ZPA). It is believed that Shh signaling from ZPA controls Anterior-Posterior patterning of the hand and digit formation. On the other hand, transcriptional activator GLI3 (Gli3) is the downstream of transcription factors of the Shh pathway and it acts as a negative regulator of posteriorization. The normal function of Gli3 is to mediate the suppression of polydactyly. So, it is suggested that the Shh/Gli pathway is to regulate digit number and identity. After the digital rays are formed, the interdigital web space is formed due to physiologically programmed cell death between the digital rays. Hand outline is nearly completed at about 7 weeks of embryonic age.

2. CONGENITAL CONSTRUCTION BAND SYNDROME

Constriction band syndrome is one of the causes of congenital absence of digits. Constriction band syndrome has four types of expressions, such as, constriction ring, lymphedema associated with constriction ring, acrosyndactyly and amputation (Fig. 1) (32). These deformities appear in various combinations. If the patient has one of these deformities, it can be diagnosed as constriction band syndrome. And, hand deformities are described with combination of these expressions.

Acrosyndactyly is called fenestrated syndactyly, in which distal part of syndactyly is deformed and fenestrations between the digits are often observed. The amputation may extend from the digital tip to the proximal part of the limb and the digits
are more often affected than the forearm and/or the upper arm. The amputation of constriction band syndrome looks like traumatic one and no bone dysplasia was found in the affected limb proximal to the amputated part (23).

There are two proposed theories for the cause of constriction band syndrome.

One is the localized cell death of the hand plate, and the other is related to amniotic constriction. In the former theory, it is postulated that the constriction band is a developmental and ischemic deficiency of the subcutis. In the later theory, it is postulated that the pressure at the edges of the amnion on the limbs when the limbs burst out from the amnion, cause the constriction by accretion of the amnion and the hand of the fetus. Kino (10) in 1975 punctured the amniotic sac in rats and induced the constriction band syndrome in animal experiments. The result was that bleeding inside the hand plate might cause the necrosis of the subcutis, and this was associated with the abnormal shrinking of the wound. Conversely, Light (12) reported: The variable clinical manifestations of congenital constriction band syndrome support the concept of local compression. On the other hand, there have been some reports that may support an intrinsic mechanism for amniotic band sequence (33), because constriction band syndrome is often associated with birth defects (such as typical cleft lip and palate), that are not readily explained by both theories. It is still not clear that constriction band syndrome is caused by a single factor. However, constriction band syndrome does appear after the formation of the digital rays.

![Fig. 2: Radial deficiency in clinical cases – A: hypoplasia of the radius, B: partial aplasia of the radius, C: total aplasia of the radius (Reprint from Ogino T. Clinical features and teratogenic mechanisms of congenital absence of digits. Dev. Growth Differ. 49: 523-531, 2007.)](image-url)
3. LONGITUDINAL DEFICIENCY

In IFSSH classification, there are two major categories of congenital absence of digits. One is transverse deficiency and the other is longitudinal deficiency.

Congenital absence of digits confined to the long axis of the upper limb is called longitudinal deficiency. In longitudinal deficiency, the absence of digits on the ulnar side is called ulnar deficiency, that of the radial side is called radial deficiency, and that of the central part is called central deficiency or cleft hand. However, many investigators suggested that teratogenic mechanisms of central deficiency were different from those of radial and ulnar deficiencies (6, 15, 20, 21, 27). Therefore, the author classified longitudinal deficiency into radial and ulnar deficiencies (29).

3.1 Radial deficiency

In radial deficiency, the skeletal changes appear in the hand, forearm and elbow in clinical cases. In the forearm, there are 4 types of dysplasia of the radius, such as total absence of the radius, partial absence of the radius, hypoplastic radius and normal radius with hypoplastic thumb (Fig. 2). Hand deformities in radial deficiency are classified according to Blauth classification (3). In his classification, Grade 1: the mildest form and hypoplasia of the thenar muscles without functional disturbance, Grade 2: hypoplasia of the thenar muscles associated with adduction contracture of the thumb, Grade 3: hypoplasia of the thenar muscles with absence of the first metacarpal base, Grade 4: floating thumb, Grade 5: the most severe form, total absence of the thumb. Non-opposable triphalangeal thumb, which is called five-fingered hand, is also one of the types of hypoplastic

Fig. 3: Ulnar deficiency in clinical cases – A: hypoplasia of the ulna, B: partial aplasia of the ulna, C: total aplasia of the ulna. (Reprint from Ogino T. Clinical features and teratogenic mechanisms of congenital absence of digits. Dev. Growth Differ. 49: 523-531, 2007.)
**Fig. 4:** Hand deformities of ulnar deficiency in clinical cases – A: hypoplasia of the little finger, B: absence of the little finger, C: absence of the 2 ulnar finger rays, D: absence of the 3 ulnar finger rays, E: absence of all finger rays. (Reprint from Ogino T. Clinical features and teratogenic mechanisms of congenital absence of digits. Dev. Growth Differ. 49: 523-531, 2007.)

**Fig. 5:** Radial deficiency induced by busulfan in rats – A: total aplasia of the radius, B: partial aplasia of the radius, C: hypoplasia of the radius, D: hypoplastic thumb with normal radius (reprinted from Kato H, Ogino T, et al. Experimental study on radial ray deficiency. J Hand Surgery 15B: 470-476, 1990)
thumb. In some cases, radial two digits such as, the thumb and index finger are absent. These deformities may appear with or without dysplasia of the radius. Radial deficiency is sometimes associated with elbow deformities. Limitation of the elbow flexion, ankylosis of the elbow, radial head dislocation and radio-ulnar synostosis may be associated with radial deficiency (9).

### 3.2 Ulnar deficiency

In ulnar deficiency, the skeletal changes appear in the hand, forearm and elbow as in radial deficiency in clinical cases. In the forearm, there are 4 types of dysplasia of the ulna, such as total absence of the ulna, partial absence of the ulna, hypoplastic ulna and normal ulna with hypoplasia or aplasia of the ulnar digits (Fig. 3). Hand deformities in ulna deficiency are classified according to Ogino's classification (Fig. 4) (25). In his classification, Grade 1: hypoplasia of the little finger, Grade 2: absence of the little finger, Grade 3: absence of the little and ring fingers, Grade 4: absence of the little, ring and middle fingers, Grade 5: absence of the little, ring, middle, and index fingers. The thumb is always preserved in ulnar deficiency. These deformities may appear with or without dysplasia of the ulna. When the dysplasia of the ulna is severe, ulnar deficiency is often associated with elbow deformities including radio-humeral synostosis or synchondrosis, radial head dislocation and severe flexion contracture of the elbow.

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**Fig. 6:** Ulnar deficiency induced by busulfan in rats – A: hypoplasia of the little finger, B: absence of the little finger, C: absence of the ring and little fingers with partial aplasia of the ulna, D, E: absence of the three and four ulnar digits with total aplasia of the ulna (reprinted from Ogino T, Kato H. Clinical and experimental studies on ulnar ray deficiency. Handchir. Mikrochir. Plast. Chir. 20:330-337, 1988)
3.3 Experimentally induced longitudinal deficiencies

In order to make an animal model of longitudinal deficiencies, the authors tried to induce longitudinal deficiency in rat fetuses by maternal administration of busulfan (9, 25). The authors could induce radial and ulnar deficiencies in rats fetuses. Characteristic features of the deformities of the limbs of longitudinal deficiency induced in rats are similar to those of clinical cases (Fig. 5, 6).

The radial deficiency could be induced only when busulfan was given on day 10 through 11 of pregnancy and the ulnar deficiency could be induced only when busulfan was given on day 9 through 10 of pregnancy. In rats used in this study, the limb bud formation starts on 12 day of gestation. The critical period of ulnar deficiency in rats is about one day earlier than that of radial deficiency. Therefore, ulnar and radial deficiencies are induced by the insult to the embryo before the limb bud is formed.

The authors compared the teratogenic conditions of ulnar and radial deficiencies. In these studies, radial and ulnar deficiencies were induced in rat by the same drug. However, the strain of rat differs. Radial deficiency was induced only in WKAH/Hkm rats and ulnar deficiency was induced only in Wistar:Gun rats. Strains of rats, in which radial and ulnar deficiencies were induced, differed. Strain susceptibility was

![Fig. 7: Cleft hand with absence of the middle finger – in roentgenogram, it is difficult to differentiate this from proximal phalangeal type of osseous syndactyly of the middle and ring fingers. (Reprint from Ogino T. Clinical features and teratogenic mechanisms of congenital absence of digits. Dev. Growth Differ. 49: 523-531, 2007.)](image-url)
observed in teratogenesis of radial and ulnar deficiencies. Thus, genetic factors influence teratogenesis of longitudinal deficiencies in rats. They also may play an important role in the genesis of longitudinal deficiencies in clinical cases.

Next, the authors histologically observed the formation of the digital rays of longitudinal deficiency in rats (24). This analysis showed that the characteristic findings of longitudinal deficiency in rats were that dead cells of mesoderm were scattered in limb-buds, the size of limb bud was smaller than control and the density of mesenchymal cells of limb-bud was lower than that in control. There was no anatomical relationship between the distribution of dead cells and the place where digits were missing. The results suggested that absence of the digits in longitudinal deficiency was not caused by the localized damage of the limb-bud. It seems that the cause of missing digits in longitudinal deficiency is closely related to deficit of mesenchymal cells in the limb bud.

FGF8 from the AER maintains the underlying mesoderm in an undifferentiated state and contribute to growth of the hand plate. Shh signaling from ZPA plays an important role in digit formation and Bmp-4 expression in the hand plate mesenchyme may control the program cell death and contribute digital formation. Then, the authors observed the expression of FGF 8, Shh and BMP 4 in the limb bud and foot plate of the preaxial longitudinal deficiency in rats by using whole-mount RNA in situ hybridization (31).

Expression of FGF 8 in the ectoderm and BMP 4 in the mesoderm were reduced. These abnormalities may cause hypoplasia of the limb. BMP 4 expression was markedly reduced in the anterior mesenchyme and Shh expression was detected in the posterior mesenchyme. These results suggested that the posterior skeletal elements may be fully formed owing to Shh expression, but the anterior skeletal elements may be underdeveloped owing to an intense reduction of BMP 4 expression in the anterior mesenchyme, causing hypoplasia of the preaxial longitudinal deficiency in rats. The combined effects of increased cell death, decreased cell proliferation, reduction of FGF 8 expression, and intense reduction of BMP 4 expression in the anterior mesenchyme may play an important role in the development of the preaxial longitudinal deficiency induced by busulfan (31).

4. CLEFT HAND

Cleft hand is defined as central deficiency under the category of failure of formation of parts in the Swanson’s classification. Central deficiency is a form of congenital absence of one or more digits in which the central rays of the hand are affected. Barsky (1) classified cleft hand into two types, one was typical cleft hand and the other was atypical cleft hand. Atypical cleft hand is a severe anomaly in which the three central finger rays are missing. In this type, sometimes there are rudiments of the missing fingers along the web between the thumb and little finger. Atypical cleft hand is considered to be a severe deformity of symbrachydactyly and it must be excluded from cleft hand. The Congenital Committee of the International Federation of Societies for Surgery of the Hand approved the recommendation that use of the term “Atypical Cleft Hand” be discontinued (14). The term “Symbrachydactyly” will be preferred to
identify this condition. Typical cleft hand is characterized by a deep V-shaped defect in the central part of the hand. In this paper, cleft hand means typical cleft hand.

4.1 Cleft hand in clinical cases

In cleft hand, there are some cases, in which polydactyly, syndactyly and cleft hand are associated in various combinations of both hands of a patient (22). These anomalies may occur in the members of the same family (13). There are also some cases, in which the middle finger is missing from the appearance but in X-ray film, the middle and ring fingers seem to be fused (Fig. 7) (15). In some cases, the middle finger is missing from the appearance, but the metacarpus of the middle finger seems to be duplicated (Fig. 8) (8, 20). From these facts, it was suggested that the abnormal induction of the number of digital rays in the hand plate induced central polydactyly, osseous syndactyly and also cleft hand (Fig. 9). When one looks at the radiographs of the clinical cases, in the case of osseous syndactyly between the middle and ring fingers, and the polydactyly of the middle finger, if the development of osseous syndactyly occurs in the proximal direction, then it will develop towards the cleft hands (Fig. 10, 11A, B) (21, 27). These observations supported the concept that a common etiological mechanism is involved in the development of central polydactyly, cleft hand and syndactyly (Fig. 9) (27, 38).

On the other hand, split hand foot malformation (SHFM) known as central ray deficiency can occur as an isolated malformation or in association with other malformations, as in the ectrodactyly ectodermal
Fig. 9: Cleft hand formation processes from central polydactyly and/or osseous syndactyly. (reprinted from Ogino T. Clinical and experimental studies on teratogenic mechanisms of the cleft hand, polydactyly and syndactyly. J Jpn Orthop Assoc 1979; 53:1753-60)
dysplasia-clefting (EEC) syndrome. The central deficiency in SHFM patients can also be accompanied by other distal limb anomalies including polydactyly and/or syndactyly.

4.2 Experimentally induced cleft hand model

In order to support this theory, the authors induced cleft hand, central polydactyly and osseous syndactyly in rat fetuses by busulfan. The deformities could be arranged in order of the severity of osseous fusion. In this way, the cleft hand formation process from osseous syndactyly and central polydactyly could be postulated (21, 27) (Figs 12, 13). It is also clear that the time (critical period) in which the cleft hand appears is consistent with that of the central polydactyly and syndactyly. A single cause affecting the limb bud in a certain receptive period of the development of the limb-bud can induce central polydactyly, cleft hand and syndactyly.

In order to examine the underlying mechanism of busulfan-induced cleft hand, central polydactyly, and syndactyly, the authors used cleft foot as a model of cleft hand and evaluated localized apoptosis by Nile Blue (NB) staining and TdT-mediated dUTP nick end labeling (TUNEL) assays in treated rat embryos. The authors further evaluated the potential disruption of major developmental pathways linked to digit number and syndactyly using FGF 8, BMP 4, and Shh as markers of these pathways (18, 19). In busulfan-treated embryos, there was no difference of expression of FGF 8, BMP 4, and Shh in the limb bud and footplate. The early morphological changes leading to central polydactyly, syndactyly, and cleft hand or foot were growth reduction and abnormal clefts in the central parts of the footplates (18). The abnormal cleft was induced.
without precedent cell death and the cleft became deeper without cell death (Fig. 14). If the abnormal cleft is induced on the edge of digital radiation, it might induce polydactyly or cleft hand or foot (Fig. 15). If the abnormal cleft is induced on the interdigital tissue, it might induce syndactyly or cleft hand or foot (Fig. 15). The authors conclude that the abnormal cleft formation without precedent cell...
death was early change leading to central polydactyly, syndactyly, and cleft hand or foot by teratogen. The abnormal cleft formation without precedent cell death might be caused by localized failure of ridge maintenance activity (18).

Results of recent studies on split-hand/split-foot malformation (SHFM) using murine Dactylaplasia mutant (Dac) have shown that the central segment of the apical ectodermal ridge (AER) degenerates, leaving the anterior and posterior segments intact. From these facts, it was suggested that localized failure of ridge maintenance activity was the fundamental developmental defect in Dac and it might also be suggested in SHFM in which phenotypes include cleft hand, syndactyly and polydactyly (7).

Because they have a similar reason of causation, cleft hand, syndactyly and central polydactyly should be included into the same entity that is abnormal induction of the digital rays. Recent literature has reported that chromosome abnormality and also abnormalities of the positional gene may cause these anomalies (5, 11, 17). These facts supported the authors’ concept. When classifying congenital anomalies of the hand based on teratogenic mechanisms, central deficiency, osseous syndactyly, and cleft hand may be grouped together, and are included in the same category of abnormal induction of digital rays (27, 29). As central polydactyly, syndactyly and cleft hand might be caused by the same teratogenic mechanism, the authors modified the IFSSH classification and added a 4th new category that is abnormal induction of digital rays and it was adapted by the Japanese Society for Surgery of the Hand and now it is called Japanese modification. As a skin manifestation, there are syndactyly and cleft of the
palm. As a skeletal manifestation, there are osseous syndactyly, central polydactyly, and absence of central finger rays (cleft hand), and triphalangeal thumb associated with cleft hand. The deformities of this category can be expressed with the combination among these deformities.

5. **TRANSVERSE DEFICIENCY**

In contrast with the longitudinal deficiency which occurs locally on the long axis of the upper limbs, the anomalies across the upper limbs which are caused by dysplasia are called transverse deficiencies. Transverse deficiency is synonymous with symbrachydactyly.

Müller (16) showed different grades of symbrachydactyly in his text book and described the concept of symbrachydactyly, which is called “skeletogene Ektrodaktylie”. Blauth & Gekeler (4) also reported a process in which deficiency of the middle phalanges in the central finger rays develops to form a symbrachydactyly. As hypoplasia of the bone develops gradually to the proximal part in the same mechanism of formation of symbrachydactyly, it eventually forms atypical cleft hand or transverse deficiency. In German speaking areas, transverse deficiency is regarded as an anomaly in the same category as short webbed finger (brachysyndactyly), atypical cleft hand and adactyly, and these anomalies are called symbrachydactyly by Müller (16), Blauth and Gekeler (4).

According to the classification by Blauth (4), grade 1 consists of short webbed finger type. Sugiura (34) classified the short webbed finger type into three

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**Fig. 13**: The skeletal changes of P-3 type of polysyndactyly induced in rats – they seem to show the cleft hand formation process from central polydactilies as in clinical cases. (reprinted from Ogino T. Teratogenic relationship between polydactyly, syndactyly and cleft hand. J Hand Surg 1990; 15B: 201–209.).

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types, such as: triphalangeal type, diphalangeal type, and monophalangeal type. The typical brachysyndactyly has short or absent middle phalanges of the fingers associated cutaneous syndactyly, while in the most severe form, there is absence of the middle and proximal phalanges of the fingers. Grade 2 is called the atypical cleft hand or two digit type, in which three central finger are absent. Grade 3 is monodactyly type in which the thumb remains and all fingers are absent (Fig. 16). Grade 4 is the peromelia type, in which all digits including thumb are absent. In grade 2, 3, and 4, there could be vestigial fingers or vestigial nails where the digits are missing.

The authors analysed their own 129 cases of symbrachydactyly and found that

Fig. 14: Early Morphologic Effect of Busulfan – at embryonic day 15 (E15), abnormal clefts in the central part of the footplate were observed (B, arrows). Although cell death was detected in the anterior and posterior mesenchyme subjacent to the AER in busulfan-exposed embryos (B, arrowheads), cell death was not detected underlying in the central portion (with respects to the anterioposterior axis) of the distal limb in contrast to age-matched controls (A, arrowheads). At E16, cell death was not detected in the area of abnormal clefting (D, arrow) and strikingly absent or reduced neighboring interdigital tissue (D, arrowheads) compared to controls (C, arrow heads). (Reprint from Naruse T, et al. Busulfan-induced central polydactyly, syndactyly and cleft hand or foot: a common mechanism of disruption leads to divergent phenotypes. Dev. Growth Differ. 49: 533–541, 2007.)
among different types, there are intermediate types of anomalies. The most characteristic feature in the roentgenograms of transverse deficiency was that various degrees of bone hypoplasia existed in the affected fingers, adjacent fingers and a proximal part of the affected limbs. The common features of all types of transverse deficiency were that all cases were unilateral, and in every grade there were some cases associated with the absence of pectoral muscle.

Finger reduction occurred mainly in the central digital rays and it had a definite pattern that progressed from brachymesophalangy, through the absence of the middle phalanx, that of the proximal and middle phalanges and that of all phalanges, finally to absence of the metacarpal bone (26). According to these observations, the sequence of anomalies from brachysyndactyly, or the atypical cleft hand, to the congenital amputation, as suggested by Blauth and Gekeler (4), can

![Abnormal induction of digital rays](image)

**Fig. 15**: Abnormal induction of digital rays – the early morphological changes leading to central polydactyly, syndactyly, and cleft hand were growth reduction and abnormal clefts in the central parts of the hand plates. The abnormal cleft was induced without precedent cell death and the cleft became deeper without cell death. If the abnormal cleft is induced on the edge of digital radiation, it might induce polydactyly or cleft hand. If the abnormal cleft is induced on the interdigital tissue, it might induce syndactyly or cleft hand.
be regarded as equivalent to the category of bony dysplasia of the hand.

This anomaly has not been induced with animal experiments and the cause of transverse deficiency is still unknown. There is no proven hereditary tendency. Developmental arrest and defect of mesenchymal cells in the hand plate are considered to be the cause because the hand of transverse deficiency is hypoplastic. The observation of the digital formation process in brachypodism mice, in which growth/differentiation factor 5 is absent genetically and the middle phalanges of all fingers are clinically absent, showed apoptosis in the digital radiations in the

Fig. 16: Transverse deficiency according to the classification by Blauth – ① Grade 1 is brachysyndactyly that is short webbed fingers. ② Grade 2 is atypical cleft hand or two digit type, in which three central digital rays are absent. ③ Grade 3 is monodactyly type, in which all digits except thumb are absent. ④ Grade 4 is the peromelia type, in which all digits are absent. (Reprint from Ogino T. Clinical features and teratogenic mechanisms of congenital absence of digits. Dev. Growth Differ. 49: 523-531, 2007.)
hand plate (37). On the other hand, it has been reported that the velocity of the systolic increase in the arterial volume decreased in the affected limb of Poland syndrome (2). On the basis of these findings, it is considered that subclavian artery supply disruption at the early developmental stage may cause Poland syndrome. Mostly the hand anomalies associated with Poland syndrome are symbrachydactyly. Therefore, there is a possibility that transverse deficiency is also caused by the same mechanism, because the hand anomalies in Poland syndrome and those of transverse deficiency are similar.

CONCLUSIONS

The author has described the teratogenic mechanisms of congenital absence of digits. The cause and teratogenic mechanism of each type of congenital absence of the digits are still unknown. However, there should be at least four different types of teratogenic mechanisms of congenital defect of the digits. The first one is longitudinal deficiencies due to mesenchymal cell death in an early developmental stage; the second is abnormal induction of digital rays including cleft hand. The third is constriction band syndrome, which is caused after digital radiations have been formed, and the fourth is transverse deficiency, in which the critical period is not known.

From the point of view for surgical management, it may convenient to adopt the classification of congenital anomalies of the hand based on morphology. The classification based on teratogenic mechanisms is convenient for monitoring congenital anomalies and in preventive medicine. However, when more is known about the developmental pathology, an ideal classification based on both genetics and morphology could be developed.

Acknowledgement

I would like to express my sincere gratitude to Hiroyuki Kato, MD, PhD, Itaru Ohshio MD, PhD, Msatoshi Takahara, MD, PhD, Takuji Naruse, MD, PhD, and Miwako Ohtuji, MD, PhD, who were my co-workers who worked hard to do animal experi-

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<th><strong>Abbreviation</strong></th>
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<tr>
<td>IFSSH</td>
<td>International Federation of Society for Surgery of the Hand</td>
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<tr>
<td>AER</td>
<td>apical ectodermal ridge</td>
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<td>FGF</td>
<td>fibroblast growth factor</td>
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<td>Shh</td>
<td>sonic hedgehog</td>
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<td>ZPA</td>
<td>zone of polarizing activity</td>
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<td>Gli</td>
<td>Transcriptional activator GLI3</td>
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<tr>
<td>WKAH/Hkm and WIstar/Gun</td>
<td>names of the strains of rats</td>
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<td>SHFM</td>
<td>split hand foot malformation</td>
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<td>EEC syndrome</td>
<td>ectrodactyly ectodermal dysplasia-clefting syndrome</td>
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<tr>
<td>TUNEL</td>
<td>TdT-mediated dUTP nick end labeling</td>
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<td>Dac</td>
<td>murine Dactylaplasia mutant</td>
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<td>E (in Fig. 14)</td>
<td>Embryonic day</td>
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**Table 1** Table for abbreviations
ments, and also to my wife, Tomoko Ogino, who supported to prepare all my studies.

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