

## REVIEW

# Perspectives on hyperphalangy: patterns and processes

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## Abstract

Hyperphalangy is a digit morphology in which increased numbers of phalanges are arranged linearly within a digit beyond the plesiomorphic condition. We analyse patterns and processes of hyperphalangy by considering previous definitions and occurrences of hyperphalangy among terrestrial and secondarily aquatic extant and fossil taxa (cetaceans, ichthyosaurs, plesiosaurs and mosasaurs), and recent studies that elucidate the factors involved in terrestrial autopod joint induction. Extreme hyperphalangy, defined as exceeding a threshold condition of 4/6/6/6/6, is shown only to be found among secondarily aquatic vertebrates with a flipper limb morphology. Based on this definition, hyperphalangy occurs exclusively in digits II and III among extant cetaceans. Previous reports of cetacean embryos having more phalanges than adults is clarified and shown to be based on cartilaginous elements not ossified phalanges. Developmental prerequisites for hyperphalangy include lack of cell death in interdigital mesoderm (producing a flipper limb) and maintenance of a secondary apical ectodermal ridge (AER), which initiates digit elongation and extra joint patterning. Factors of the limb-patterning pathways located in the interdigital mesoderm, including bone morphogenetic proteins (BMPs), BMP antagonists, fibroblast growth factors (FGFs), growth/differentiation factor-5 (GDF-5), *Wnt-14* and *ck-erg*, are implicated in maintenance of the flipper limb, secondary AER formation, digit elongation and additional joint induction leading to hyperphalangy.

**Key words** Limb; autopod; skeleton; evolution; development; polyphalangy; cetacea; ichthyosaur.

## Introduction

Although some recent studies have considered a phylogenetic pattern of hyperphalangy (Richardson & Oeschläger, 2002; Richardson & Chipman, 2003), development of the cetacean forelimb in general (Sedmera et al. 1997; Sterba et al. 2000) or evolutionary reduction of cetacean hindlimbs (Bejder & Hall, 2002), additional observations and theoretical considerations are warranted and provided here to extend these studies. We analyse patterns and processes of hyperphalangy by considering previous definitions and occurrences of hyperphalangy among terrestrial and secondarily aquatic extant and fossil taxa (cetaceans, ichthyosaurs, plesiosaurs and mosasaurs), and recent studies that elucidate the factors involved in terrestrial autopod

joint induction. Development and evolution of hyperphalangy is fundamentally about patterning of the joints within the autopod; the number of joints formed within the digit determines the number of phalanges. Recent progress that provides insight into the factors involved in joint induction among terrestrial taxa is considered to provide possible directions for future work on cetacean limb development.

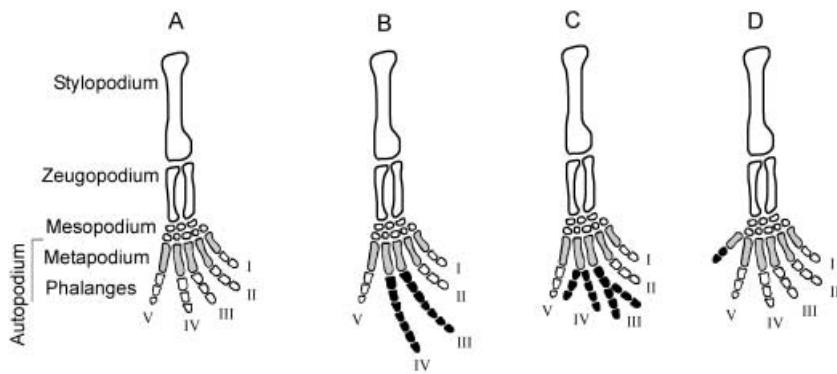
Hyperphalangy is a digit morphology wherein the number of phalanges arranged linearly within an individual digit is increased above the plesiomorphic condition (Fig. 1B). Polyphalangy is often used synonymously with hyperphalangy. However, we use polyphalangy, as in Meteyer (2000), to refer to branched digit morphologies, in which an extra row of phalanges is associated with a metapodial element (Fig. 1C). This distinguishes phalanges added co-linearly (hyperphalangy) and adjacently (polyphalangy), to acknowledge that each of these morphologies may result from different processes or have unique functional or selective attributes. Some uncertainty remains as to whether

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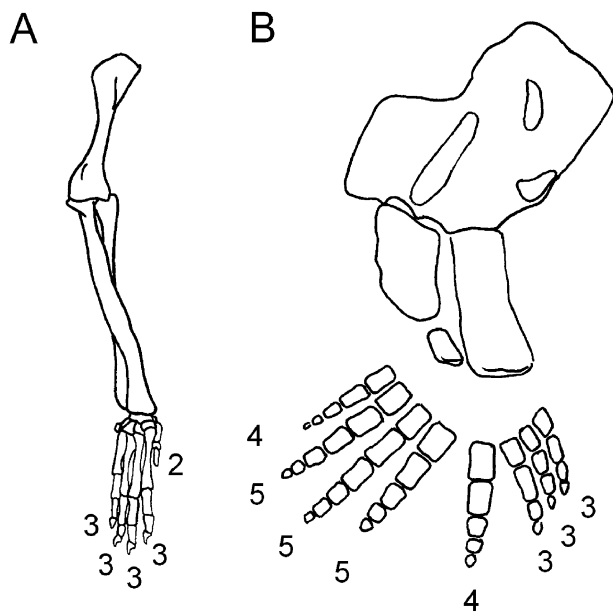
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**Fig. 1** Diagrammatic right forelimbs in anterior view. (A) From proximal to distal, the tetrapod limb is composed of the stylopodium, zeugopodium, mesopodium, metapodium (grey shading) and phalanges. Together, the metapodium and phalanges are referred to as the autopodium. Shown here is a typical mammalian autopod with the phalangeal formula 2/3/3/3/3. Other theoretical limbs demonstrate (B) hyperphalangy (digits III–IV), (C) polyphalangy (digits III and IV), and (D) a polydactalous autopod with one extra digit.



**Fig. 2** (A) The right forelimb of a cat exhibits the typical terrestrial mammalian phalangeal formula 2/3/3/3/3. (B) The pentadactyl limb evolved probably from an ancestral eight-digit ancestor similar to *Acanthostega*, which shows a phalangeal formula 3/3/3/4/5/5/5/4. The mesopodial elements (carpals) are not known in the ancestral tetrapod *Acanthostega*, they were presumably cartilaginous and did not fossilize. A – modified from Liem et al. (2001), B – modified from Coates & Clack (1990).

polyphalangy results from an extra developmental branching event or formation of a phalangeal row *de novo* (Shubin & Alberch, 1986; Cohn et al. 2002). With polyphalangy, both phalangeal rows might contact the same metapodial element (Fig. 1C – digit IV) or the phalangeal rows may diverge mid-digit, and thus contact a phalanx proximally (Fig. 1C – digit III).

A third modification to digit morphology seen in some tetrapods including some cetacean flippers is polydactyly (Fig. 1D), which designates the addition of

an extra metapodial element beyond the plesiomorphic condition. This extra metapodial might or might not have phalanges distally.

Padian (1992) presented a system to describe the distribution of phalanges within the autopod. Digits are listed medial to lateral (I/II/III/IV/V), by the number of phalanges present. We account for intrataxa variation in phalangeal formulae of a digit by listing the range observed (e.g. 3–4) for the variable digit and therefore separate each digit by a slash, '/'. The highly conserved terrestrial mammalian phalangeal formula can be represented as 2/3/3/3/3 (Fig. 2A). When a metapodial lacks phalanges, the digit is scored with a '0'; if no metapodial or phalanges are present the absence of the digit is scored with an 'X'.

### Terrestrial hyperphalangy

Increases in phalangeal number are rare among terrestrial amniotes. The trend is towards a reduction in the number of both digits and phalanges from the ancestral amniote formula of 2/3/4/5/4 (Carroll, 1988), such as the terrestrial mammalian formula 2/3/3/3/3.

Identification of phalangeal formulae in the literature is not always based strictly on adult ossified elements. The phalangeal formula for *Alligator mississippiensis* has been shown to be 2/3/4/5/4 (manus) and 2/3/4/5/0 (pes), not the previously accepted formula (2/3/4/3/2) based on ossified elements of both the manus and the pes in adults (Romer & Parsons, 1977); the distal-most phalanges of digits IV and V do not ossify (Müller & Alberch, 1990). Distinction between cartilaginous and ossified phalanges is crucial for discussions of hyperphalangy. Counting of cartilaginous phalangeal elements is difficult in extant material and impossible among fossil taxa. Therefore, only ossified elements are considered

**Table 1** Squamate taxa that exhibit increases in phalangeal number above the plesiomorphic condition (modified from Greer (1992) and Greer & Smith (1999). Underlined values represent additions of only a single phalanx beyond the plesiomorphic condition

Taxa	Manus	Pes	Other Information
<b>Plesiomorphic condition</b>	2/3/4/5/3	2/3/4/5/4	
<i>Ctenophorus femoralis</i>		2/3/4/ <u>6</u> /4	
<i>Tympanocryptis tetraporophora</i>	2/3/4/ <u>6</u> /3		Only 1 of 61 specimens showed the additional phalanx. Gans (1978).
<i>Bipes biporus</i>	<u>3</u> /3/3/3/3		
<i>Chondrodactylus</i>	<u>3</u> /3/4/5/3	<u>3</u> /3/4/5/4	
<i>Narudia festiva</i>	2/3/4/5/ <u>4</u>		
<i>Lerista dorsalis</i>	0/2/2/ <u>6</u> /4		
<i>Scincus scincus</i>	2/3/4/5/ <u>4</u>	2/3/4/5/ <u>5</u>	

true phalanges for this study, and phalangeal formulae are based on ossified elements unless otherwise stated.

Based on the ancestral squamate phalangeal formula 2/3/4/5/3 (manus) and 2/3/4/5/4 (pes), Greer (1992) and Greer & Smith (1999) identified rare phalanx additions among several terrestrial squamate taxa (Table 1). While considering the functional significance of increased numbers of phalanges, Greer (1992) noted that all increases occur on the margins of the autopod (Table 1), and proposed functional advantages for extended foot reach and improved digging. However, as digit length data were not provided, it is uncertain if digit length correlates with an increase in the number of phalanges. The distinction between digit length and phalangeal number is important; if the number of phalanges/joints increased without increasing digit length, other functional explanations may be more appropriate (e.g. increased flexion). Conversely, there are many examples in which digit length increases without increasing the number of phalanges (e.g. bats, pterosaurs).

Richardson & Chipman (2003) suggest that the aquatic turtle genus, *Chitra*, with a phalangeal formula of 2/3/3/6/4, and an extensively webbed manus, represents another example of limited phalanx addition. Although there are some examples of small increases in number of phalanges among terrestrial vertebrates, the additions are small and do not appear to exceed a maximum of six phalanges in any one digit.

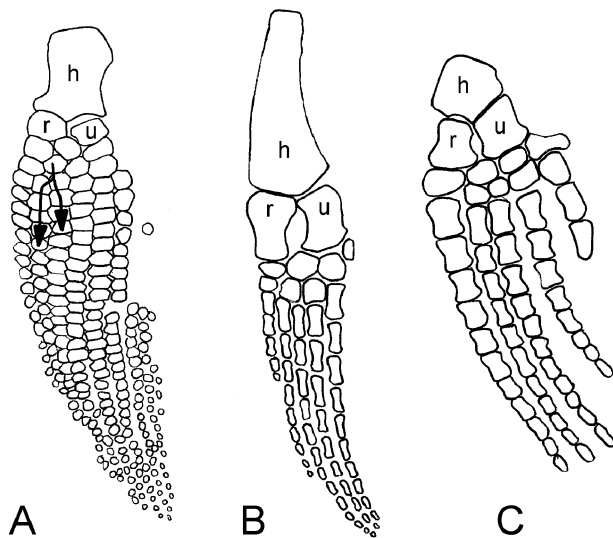
### Fossil record

Although small increases in the number of phalanges are rare among terrestrial taxa, hyperphalangy is common among several groups of secondarily aquatic amniotes and involves extreme morphological change.

Ichthyosaurs are marine diapsids from the Triassic to Late Cretaceous. Similar to modern dolphins, ichthyosaurs had a fusiform body shape, albeit with a vertical, not horizontal, orientation to the caudal tail fin. Like many aquatic vertebrates, ichthyosaurs appear to have used lateral undulation to provide thrust, employing their elongate, paddle-shaped limbs for steering (Carroll, 1988). The oldest ichthyosaurs (Lower Triassic) had an ossified phalangeal formula of 2/4/4/4/1, similar to their terrestrial tetrapod ancestors (Carroll, 1988). Later ichthyosaur taxa demonstrate extreme examples of hyperphalangy, with some digits containing over 20 phalanges (Fig. 3A). The more recent forms also demonstrate polyphalangy (Motani's 'supernumerary digits'), thought to result from branching of the digit anlagen (Motani, 1999). Numerous examples of embryonic ichthyosaur skeletal material have been recovered and demonstrate that ichthyosaurs gave live birth and were fully aquatic.

Mosasaur, another group of secondarily aquatic squamates common during the Upper Cretaceous, demonstrate hyperphalangy of pectoral and pelvic limbs (Caldwell, 2002). There is some evidence that mosasaurs gave live birth (Bell et al. 1996), and like ichthyosaurs, mosasaurs probably relied on the laterally compressed tail to provide thrust and used their elongate paddle-shaped limbs for steering (Carroll, 1988).

During a discussion of developmental constraint, Richardson & Chipman (2003) examined the broad phylogenetic distribution of hyperphalangy among amniotes. They defined hyperphalangy as any increase beyond the ancestral amniote formula 2/3/4/5/3, and then examined if hyperphalangy was co-distributed with some possible adaptive traits such as digit elongation, swimming style, digging or modes of terrestrial



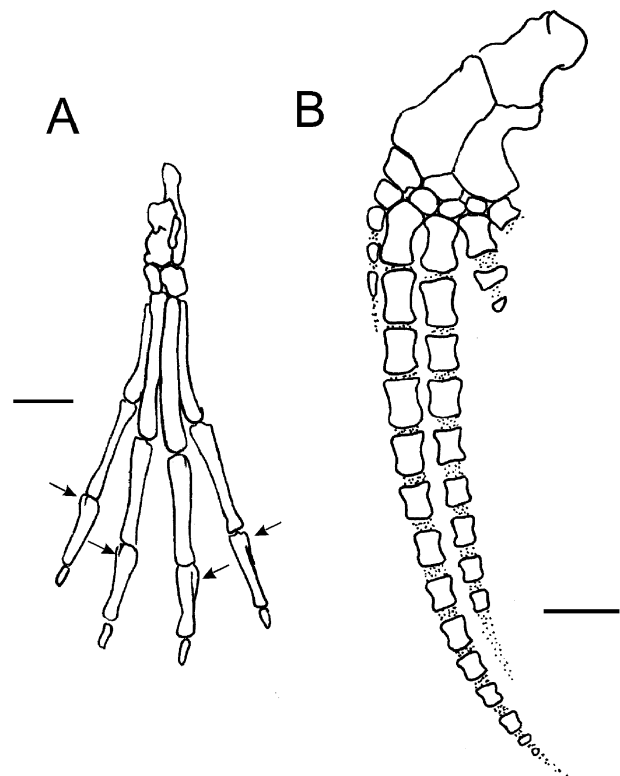
**Fig. 3** Left forelimbs of *Ichthyosaurus* (A), the Sauropterygian *Plesiosaurus brachpterygius* (B) and the Mosasaurid *Pliosaurus* (C), demonstrating extreme hyperphalangy. The arrows (A) identify a polyphalangeous (branched) digit. Limbs are not drawn to scale. Abbreviations: h – humerus, r – radius, u – ulna. A – modified from Motani (1999), B – modified from Caldwell (1997b), C – modified from Carroll (1988).

locomotion. Their study found no co-distribution that might explain the development of hyperphalangy.

However, Richardson and Chipman coded mosasaurs as not aquatic/semi-aquatic (their Fig. 3). As already mentioned, recent palaeontological work (Bell et al. 1996) suggests that mosasaurs gave live birth, similar to ichthyosaurs. Their highly derived body morphology, giving live birth, and not requiring return to land for egg laying, suggests mosasaurs were indeed (secondarily) aquatic. Contrary to Richardson and Chipman's conclusions, an aquatic habitat does co-distribute with the occurrence of hyperphalangy as they defined it. Interestingly, this suggests that terrestrial habitats may in fact constrain hyperphalangy, and that secondarily aquatic vertebrates are freed from this constraint.

### Cetacean hyperphalangy

Bejder & Hall (2002) reviewed changes in early cetacean limb morphology after the transition from terrestrial to aquatic habitats during the Eocene (52–42 million years ago). They pointed out that, although the Eocene archaeocetes (early cetaceans) show many adaptations for aquatic life, they do not demonstrate hyperphalangy. Unfortunately, little is known about the manus structure of the earliest fossil archaeocetes.



**Fig. 4** The pes of the archaeocete *Rodhocetus balochistanensis* (A); arrows show lateral and medial processes on distal phalanges (scale bar = 5 cm). The left forelimb of the round headed dolphin, *Globicephala melas* (B). The stippling represents cartilage; scale bar = 10 cm. A – modified from Gingerich et al. (2001), B – modified from Flower (1876).

The archaeocete *Rodhocetus balochistanensis* (47 Ma) demonstrates a phalangeal formula of the manus comparable with that of most modern terrestrial mammals. Medial and lateral processes on the phalanges of the pes (Fig. 4A) suggest the feet were webbed (Gingerich et al. 2001). Basilosaurids, the sister taxa to extant cetaceans, also do not demonstrate hyperphalangy (Uhen, 1998). With the recent increase of fossil cetaceans being described it will be of interest to determine if any early fossil taxa demonstrate hyperphalangy. Analysis of the distribution of hyperphalangy among extant cetaceans, however, predicts that none of the fossil forms will demonstrate this morphology (see below).

Hyperphalangy is common among extant cetaceans (Table 2) and can be extreme in some taxa, with up to 14 phalanges in the Pilot Whale, *Globicephala melas* (Fig. 4B). Unlike the highly constrained phalangeal formulae in terrestrial mammals, there is considerable variation in phalangeal counts both between and within cetacean taxa (Nishiwaki, 1972), as well as frequent

**Table 2** Body lengths and phalangeal counts for selected extant cetaceans. Phalangeal counts in bold represent hyperphalangy as defined by exceeding the threshold 4/6/6/6 and, where variable, the median value exceeds this threshold

Taxa	Common name	Length (m)	Digit					Source
			I	II	III	IV	V	
<b>Mystacoceti</b>								
<i>Balaena mysticetus</i>	Bowhead Whale	15	1	3–4	4–5	3–4	2–3	1
<i>Eschrichtius robustus</i>	Gray Whale	13		3	3	4	1	1
<i>Balaenoptera physalus</i>	Fin Whale	20	4	<b>7</b>	<b>7</b>	4		1 <sup>a</sup>
<i>Megaptera novaeangliae</i>	Humpback Whale	12	2–3	<b>7</b>	<b>6–7</b>	2–3		1 <sup>a</sup>
<b>Odontoceti</b>								
<i>Delphinapterus leucas</i>	Beluga	4	0–1	5–6	3–4	1–3	1–3	Table 3
<i>Delphinus delphis</i>	Common Dolphin	2.5	2–3	<b>8–9</b>	5–7	2–4	1–2	1
<i>Globicephala melas</i>	Pilot Whale (= melaena)	6.5	3–4	<b>9–14</b>	<b>9–11</b>	2–3	1–2	1
<i>Inia geoffrensis</i>	Amazon River Dolphin	1.5	1	5	4	2	2	2
<i>Kogia breviceps</i>	Pygmy Sperm	2.5	2	<b>5–8</b>	4–8	4–8	2–7	1
<i>Lagenorhynchus acutus</i>	Atlantic Whitesided Dolphin	2.7	1–2	<b>10</b>	6	2–3	2	1
<i>Lagenorhynchus albirostris</i>	Whitebeaked Dolphin	3	2	<b>6</b>	4	1	0	1
<i>Lagenorhynchus obliquidens</i>	Pacific Whitesided Dolphin	2.3	1–2	<b>6–8</b>	6	2–3	1–2	3
<i>Mesoplodon peruvianus</i>	Pygmy Beaked Whale	3.5	1	5	5	3	2	4
<i>Phocoena phocoena</i>	Harbour Porpoise	1.8	2–3	<b>7–8</b>	<b>6–8</b>	3–5	1–2	1
<i>Physeter catodon</i>	Sperm Whale	15	1	5	5	4	3	1
<i>Tursiops truncatus</i>	Bottlenose Dolphin	2.5	1–2	<b>7–9</b>	<b>5–8</b>	2–3	1–2	1
<i>Ziphius cavirostris</i>	Cuvier's beaked	6	1	3–6	5–6	4	1–2	1

Sources: 1 – Tomilin (1967), 2 – Flower (1866), 3 – Nishiwaki (1972) and 4 – Reyes et al. (1991).

<sup>a</sup>We follow Omura (1975) and consider *Balaenoptera* and *Megaptera* digits IV and V of previous authors (Tomilin, 1967) as representing digits III and IV (see text).

**Table 3** Various ‘phalangeal formulae’ reported in the literature for both embryonic and adult specimens of the Beluga, *Delphinapterus leucas*. The number of elements is listed for each digit. A, B and C are high, as authors included cartilaginous phalanges and metapodials. We consider F to represent the ossified phalangeal formula for the Beluga, calculated by subtracting 1 from values in D and E in order to remove the metapodial element

	Digit					Stage	Cartilage	Metapodial	Citation
	I	II	III	IV	V				
A	3	9	8	7	7	Embryos	Yes	Yes	Kleinenberg et al. (1969)
B	3	8	7	6	6	Adult	Yes	Yes	Kleinenberg et al. (1969)
C	2–3	9	7	6	6	Embryos	Yes?	Yes?	Tomilin (1997), cites Kükenthal (1893)
D	1–2	6–7	4–5	2–4	2–4	Adult	?	Yes?	Tomilin (1967), cites Kükenthal (1893)
E	1–2	6–7	4–5	2–4	2–4	Adult	?	Yes	Nishiwaki (1972)
F	0–1	5–6	3–4	1–3	1–3		No	No	

asymmetrical variation of phalangeal counts between left and right limbs in a single individual (Sedmera et al. 1997).

Ontogenetic variability has also been proposed, with the maximum number of phalanges said to occur in the late embryonic stages, rather than in adults (Bejder & Hall, 2002). True (1904, p. 143) originally took issue with this idea and considered the discrepancy to have come about when Kükenthal (1893) included metacarpals in his embryonic phalangeal counts. Kleinenberg

et al. (1969) reported that Beluga embryos have more phalanges than adults; however, their study counted metacarpals along with both cartilaginous and ossified phalanges (Table 3). Although some cartilaginous phalanges may fuse through ontogeny, it seems unlikely that the number of ossified phalanges per digit decreases as cetaceans age.

To examine the distribution of hyperphalangy among extant cetaceans, we have chosen to use a high threshold definition of hyperphalangy, in which if any



digit exceeds the phalanx state of 4/6/6/6/6, the digit is considered to represent hyperphalangy. Richardson & Chipman (2003) noted that the threshold at which authors choose to demarcate the occurrence of hyperphalangy is somewhat subjective, and certainly affected by phylogenetic hypotheses of ancestral states. We believe using a high threshold has several benefits. The high threshold clearly demarcates dramatic increases above the plesiomorphic mammalian condition (2/3/3/3/3) and tends to filter out any problems in the literature resulting from inclusion of metapodials or cartilaginous elements. In addition, a digit that exceeds six phalanges represents a new tetrapod morphology, surpassing the plesiomorphic tetrapod phalanx state of 3/3/3/4/4/5/5/4 (Fig. 2B) suggested in one of the earliest known tetrapods, *Acanthostega* (Coates & Clack, 1990).

Using data from the literature (Table 2) each of the five digits for all taxa was scored (1) for hyperphalangy if it exceeded the relevant threshold value (4/6/6/6/6), or (0) if it was equal to or less than the threshold. When the literature suggested the phalangeal count for a digit is variable (e.g. digit IV scored as 4–7), if the median value (e.g. 5.5) did not exceed the threshold value the digit was scored as not representing hyperphalangy (0). Hyperphalangy was mapped on to a cladogram to examine distribution across extant Cetacea.

Several recent phylogenies have been proposed for various subsets of Cetacea. We map hyperphalangy on to a cladogram of fossil and extant cetaceans derived from both morphological and molecular data (Messenger & McGuire, 1998). Owing to insufficient phalangeal formulae data, six taxa (*Kogia simus*, *Mesoplodon europaeus*, *Phocoena spinipinnis*, *Cephalorhynchus eutropia*, *Lagenorhynchus obscurus* and *Lissodelphis peronii*) were removed from the cladogram. The results obtained after removing these taxa are considered to represent the overall pattern across Cetacea, as each of the main nodes of the tree is represented by at least one taxon with a known phalangeal formula.

To consider how many times hyperphalangy has evolved we performed an ACCTRAN optimization (Wiley et al. 1991) for the states of each digit throughout the cladogram (Fig. 5). Using an ACCTRAN analysis ensures that reversals are favoured over parallelisms if two equally parsimonious choices are offered, providing a conservative estimate of the number of times hyperphalangy has evolved. Furthermore, it was assumed

that when more than one digit became hyperphalangeous at any position (node or branch) in the cladogram, only a single evolutionary event occurred.

The analysis shows that hyperphalangy evolved three times among extant cetaceans, with two reversals (Fig. 5). Hyperphalangy evolved separately in the Mystacoceti and Odontoceti. Based on the character distribution across extant cetaceans, hyperphalangy is not expected to be found among fossil taxa. Furthermore, hyperphalangy is found among cetaceans with both large (*Balaenoptera* and *Megaptera*) and small (*Delphinus*, *Kogia* and *Lagenorhynchus*) body sizes (Table 2). Therefore, a size-dependent factor to explain the development of hyperphalangy is not appropriate.

Some authors have considered *Balaenoptera* and *Megaptera* whales as having lost digit III (Tomilin, 1967). This would be very surprising, however, and a clear violation of a 'forbidden morphology' (Holder, 1983a). Instead we follow Omura (1975) and consider Tomilin's counts for digit IV and V to represent digits III and IV. Accounting for this, it is interesting that hyperphalangy is limited to the central digits II and III in both baleen (Mystacoceti) and toothed (Odontoceti) cetaceans. By considering the details of limb development, a hypothesis can be developed to explain the development of hyperphalangy.

### Cetacean limb development

The ability to obtain adequate embryonic material is a major challenge for conducting comparative cetacean limb development studies. The remote habitat and threatened state of many wild populations, and the problems of obtaining preparturition (embryonic) stages from live females are only the most obvious difficulties. Two scenarios would circumvent these challenges.

The first would rely on quick recovery of embryonic material from recently deceased females stranded, washed ashore or captured during fishing activity. This would require the cooperation and training of individuals who would respond to cetacean strandings. Regrettably, this sampling method would rely on chance, and it would be difficult to obtain a broad spectrum of various staged samples. Studies discussed below used collections of embryos recovered from tuna nets in the 1970s (Richardson & Oeschläger, 2002).

A second option for future developmental work would involve captive breeding populations. Between 1983 and 1991, 122 bottlenose dolphin calves (*Tursiops*

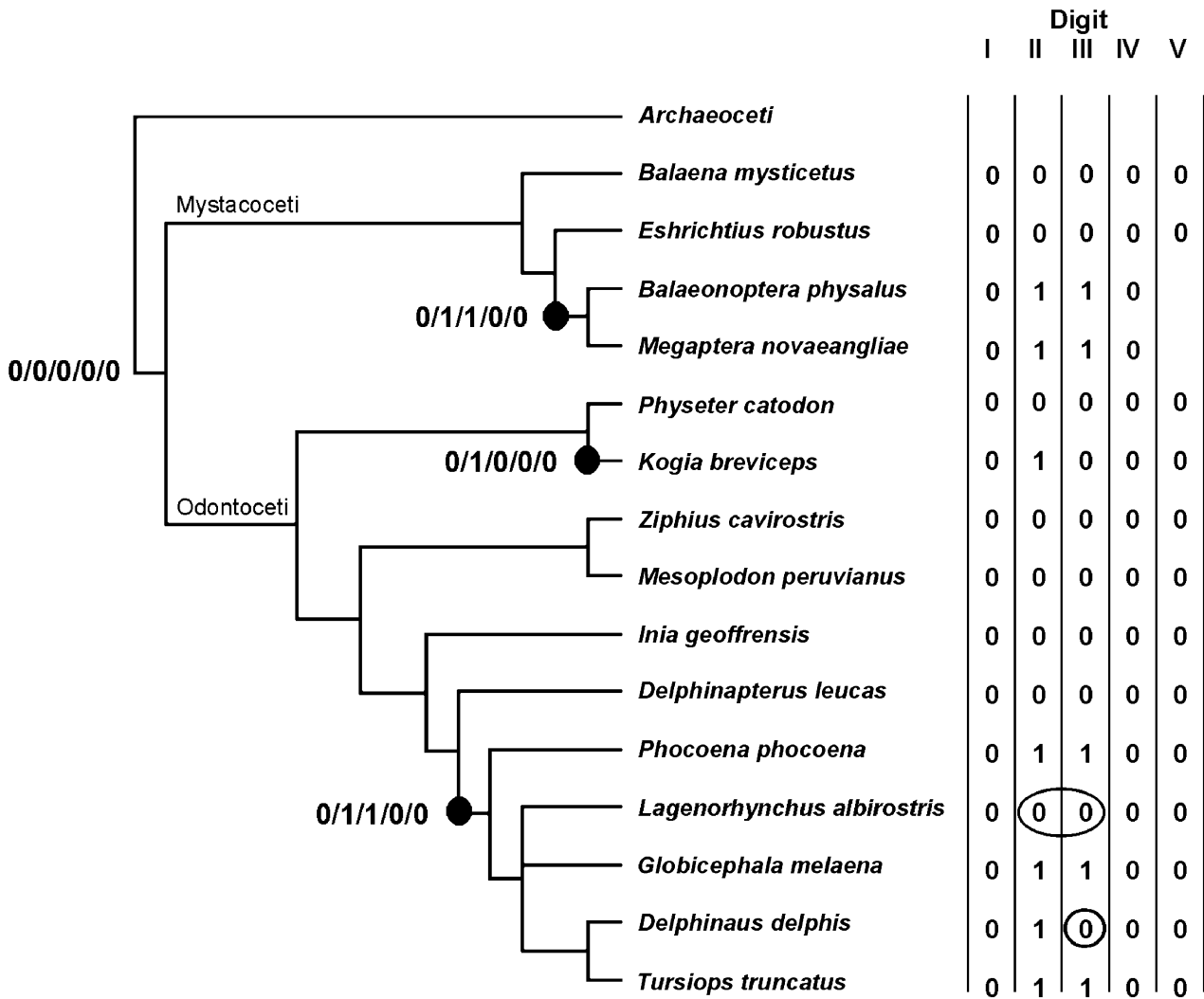


Fig. 5 Phylogenetic distribution of hyperphalangy in cetaceans, in which hyperphalangy is defined as exceeding the threshold of 4/6/6/6/6 (see text). The ACCTRAN analysis suggests hyperphalangy occurred three times (solid dots), with two reversals (open circles), and only ever involves the central digits II, III and IV.

*truncatus*) were born in captivity (Mayer, 1998). Mayer also suggests that orcas, white-sided dolphins, beluga whales and Commerson’s dolphins have conceived and given birth in captivity; however, the bottlenose dolphin appears to be the most successful captive breeder so far. As new technologies such as artificial insemination, *in vitro* fertilization and cloning are incorporated, successful breeding programmes would be expected to increase. These factors suggest bottlenose dolphins as the most likely model organism for future cetacean developmental studies.

A recently published staging guide for embryos and fetuses of several cetaceans (Sterba et al. 2000) provides some insight into details of cetacean digit development. Early on (Sterba et al. stage three), the

limb is the typical shape for terrestrial mammals. Gradually (stage five, 32–42 days), the humerus, radius, ulna and unsegmented digital rays may be observed, and the hand-plate is symmetrical along the third digit. Later still (stage six, 41–52 days), the ‘axis of the hand-plate is shifted from the third to the second ray which increases in length’ (Sterba et al. 2000, p. 100). Addition of digital phalanges in digits II and III is also noted during this stage.

Richardson & Oeschläger (2002) confirmed that the proximal elements of the white-sided dolphin autopod developed in a pattern similar to that of terrestrial vertebrates, including phalanx joint induction. However, they also showed that prolonged maintenance of a small section of apical ectodermal ridge (AER) distal to

digits II and III corresponds with the elongation of these digits after the basic (terrestrial) digital pattern had been established and the other areas of the AER regressed. Outgrowth of the limb continues during the development of hyperphalangeous limbs by maintaining a localized area of AER.

Another study of particular interest (Sedmera et al. 1997) noted absence of interdigital cell death in the forelimb during development of the white-spotted dolphin *Stenella attenuata*. Maintenance of the interdigital mesoderm appears to be significant for development of hyperphalangy when details of joint development among terrestrial vertebrates are considered.

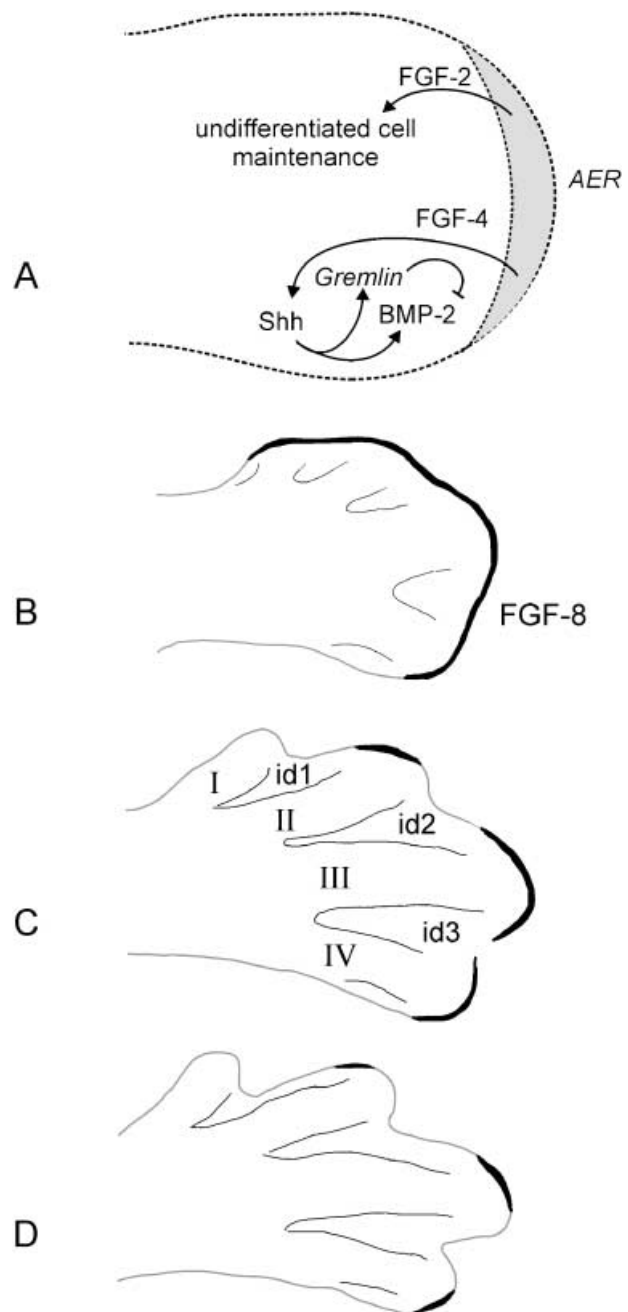
### Terrestrial digit development

Studies of terrestrial amniote (e.g. chick and mouse) limb development and joint induction provide details regarding factors likely to influence hyperphalangy. These studies detail interactions between AER maintenance, interdigital mesoderm and phalangeal joint patterning.

### Elongation

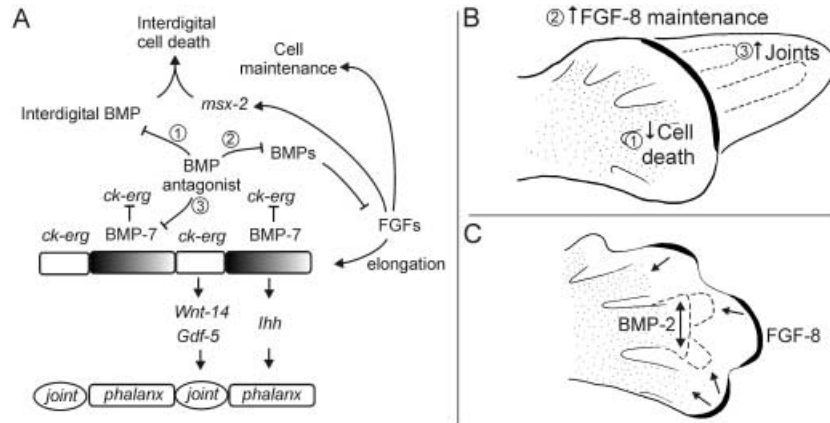
The proximodistal axis is specified at the earliest limb bud stages with the formation of the AER on the distal limb bud. Fibroblast growth factors (FGFs) from the AER (including FGF-2, FGF-4 and FGF-8) have been implicated in promoting survival and delaying differentiation of subjacent mesenchymal cells of the limb bud (Fig. 6A) (Fallon et al. 1994; Macias et al. 1996; Sun et al. 2002; Sanz-Ezquerro & Tickle, 2003). Removal of the AER ceases limb outgrowth, producing distally truncated limb morphologies. However, limb outgrowth can be rescued by local application of exogenous FGF-2 (Fallon et al. 1994). FGF-8 is broadly expressed across the AER in late stages of chick limb development, then localized above the digits during final digit elongation, finally terminating in a sequence that corresponds with increasing number of phalanges in both manus (Sanz-Ezquerro & Tickle, 2003) and pes (Gañan et al. 1998) (Fig. 6B–D).

Bone morphogenetic proteins (BMPs) are expressed broadly across early limb buds, and within the interdigital mesoderm at later stages. BMPs are involved in chondrocyte maturation and cell death induction, and limit outgrowth of the limb by promoting AER regression (Pizette & Niswander, 1999). For example,



**Fig. 6** FGFs are important signalling factors for limb and digit elongation. (A) A schematic diagram of an early right limb bud in dorsal view shows FGFs from the AER maintain the underlying mesenchymal cells and participate in the maintenance of the ZPA on the posterior distal margin of the limb. BMP antagonism (*Gremlin*) prevents BMP-induced regression of the AER and therefore maintains the Shh and FGF feedback loop. (B) At stage 30 FGF-8 (thick black line) is broadly expressed across the AER, but diminishes above the interdigital areas (id 1–3) at stage 32 (C). At stage 33, FGF-8 expression ceases above the digits in an order that corresponds with the (increasing) number of phalanges in each digit (D). B–D represent the right foot of a chick in dorsal view; redrawn from Gañan et al. (1998).





**Fig. 7** The autopod patterning pathway (A) shows the importance of BMPs and BMP antagonist interactions as well as the competitive interactions between BMPs and FGFs for the development of hyperphalangy (B). Antagonism of BMP factors could limit BMP induction of interdigital cell death (1), block BMP regression of the AER to prolong FGF expression and result in elongate anlagen (2), and to play a role in joint development by preventing BMP down-regulation of transcription factors such as *ck-erg* (3). Initially *ck-erg* is found along the entire anlagen, but becomes down-regulated by BMP-7, which is limited to areas of presumptive phalanges. Following joint induction, *Wnt-14* and *Gdf-5* are expressed in developing joints, while Indian hedgehog (*Ihh*) is up-regulated in phalanges and promotes bone development. A hypothesized explanation for the development of polyphalangy (C) suggests BMPs increase the radial diameter (double arrow) of an elongating anlagen to such a point that it becomes influenced by multiple FGF-8 signals from the AER (arrows), causing the anterior and posterior distal tip to expand in different directions (dashed lines).

the zone of polarizing activity (ZPA), located posteriorly in the limb bud directly below the AER, is responsible for anterior–posterior patterning of tetrapod limbs. Gremlin (a BMP antagonist) is required to maintain the ZPA and an FGF feedback loop from the AER (Fig. 6A), suggesting BMPs negatively regulate this pathway (Khokha et al. 2003). In addition, over-expression of the BMP antagonist Noggin results in prolonged FGF-8 expression above the digits in later stages of limb development (Pizette & Niswander, 1999). These and other studies demonstrate BMPs and FGFs work in opposition during limb outgrowth, BMPs repressing and FGFs promoting outgrowth.

Sanz-Ezquerro & Tickle (2003) propose an interesting digit elongation model in which FGF-8 localized in the AER above the digits controls digit elongation, and BMPs moderated through hedgehog signalling (*Ihh*) from limb mesenchymal cells eventually induce AER regression and cessation of FGF-8. Implanting a hedgehog (*Shh*) factor into interdigital mesoderm results in digit elongation, increased expression of BMP-2 and BMP-7, but reduced expression of BMP-4. They suggest that reduction in BMP-4 and/or up-regulation of a BMP antagonist by the exogenous hedgehog factor are responsible for FGF-8 maintenance and digit elongation. No elongation results when the *Shh* bead is implanted along with an FGF inhibitor. Interestingly, Noggin has

a stronger antagonistic effect on BMP-2 and BMP-4 than on BMP-7, and exogenous application of *Shh* into interdigital mesoderm also results in up-regulation of Noggin and down-regulation of *msx-2* (Pizette & Niswander, 1999).

Although not related to hyperphalangy, BMPs have also been shown to increase digital condensation width (Macias et al. 1997), and branched digits result from experimental application of BMP to the anterior interdigital mesoderm (Duprez et al. 1996). It is interesting to consider that digit branching (polyphalangy) may result from BMPs increasing condensation width during elongation, to an extent at which the distal condensation is influenced by multiple elongation (FGF-8) signals from the AER (Fig. 7C).

**Patterning**

The digits are the last limb elements to appear, and the metapodials and phalanges of a digit are initially continuous anlagen. Only after elongation is this anlagen segmented to produce the common digit morphology of multiple, linearly arranged phalangeal elements. There is convincing evidence that amniote phalangeal joints are patterned by interaction(s) between digital rays and factors in interdigital mesoderm. Dahn & Fallon (2000) demonstrated that digital joint pattern

is determined by signals originating from the most posterior interdigital mesoderm a digit contacts (Fig. 6C), and they considered BMPs to be the most likely agent specifying 'digit identity' (the number of phalanges).

However, it seems BMPs may negatively regulate phalanx joint formation. BMP-7 is located in the perichondrium of digital anlagen, except in areas of presumptive joints, whereas exogenous BMP-7 applied to the interdigital mesoderm results in phalangeal joint failure (Macias et al. 1997). BMP-7 is thought to down-regulate *ck-erg*, a transcription factor initially found within the perichondrium along the whole length of the anlagen, but is later restricted to areas where phalangeal joints will form (Gañan et al. 1996; Macias et al. 1997). Brunet et al. (1998) found the phalangeal joint pathway was interrupted in Noggin-deficient mice based on non-expression of growth/differentiation factor-5 (GDF-5) in mutant digits whereas *Gdf-5* was expressed in early phalangeal joints of wild-type mice.

Hartmann & Tabin (2001) demonstrated that Wnt-14 is selectively expressed in areas of presumptive joints, can induce ectopic joints in chick digital anlagen and that the ectopic joints repressed nearby normal joints. They proposed a *chordin* gradient up-regulated by Wnt-14 as a potential pathway responsible for joint repression, although no chordin gradient was demonstrated. However, a phalangeal joint spacing pathway might involve noggin antagonizing BMPs from the posterior interdigital cells and/or perichondrium, effectively spacing the *ck-erg* transcription factor, Wnt-14, Gdf-5 joint formation pathway (Fig. 7A).

### Digit separation

Following digit elongation and joint patterning, most amniotes attain separation of the digits by apoptosis of interdigital mesoderm cells (Cameron & Fallon, 1977). Initiation of interdigital cell death is concurrent with flattening of the AER; however, early removal of AER does not induce cell death. Therefore, the link is probably coincidental rather than causal (Gañan et al. 1998). BMP-4 has been implicated as the specific factor inducing interdigital cell death (Macias et al. 1997); when endogenous BMP in the chick leg was blocked with a retrovirus, reduced interdigital cell death (syndactyly) resulted (Zou & Niswander, 1996).

Gañan et al. (1998) further elaborated the roles of both BMPs and FGFs in autopods with free (chick) and webbed (duck) digits. Ducks have reduced interdigital

BMP expression, but FGF up-regulation of *msx-2*, and interdigital BMPs are required for interdigital cell death. By implanting an FGF-soaked bead into the third interdigital mesoderm of a duck, *msx* expression and interdigital cell death increased after the FGF bead expired, but cell death was maximized by co-implantation with a BMP-soaked bead. Again, limb patterning is tied to interactions between BMP (death) and FGF (maintenance) signals.

The above studies can be brought together to suggest a dynamic pathway in which joint specification, interdigital cell death and digit elongation are mediated by interactions between BMPs, BMP antagonists and FGF signalling from the AER (Fig. 7). Slight modifications of the pathway(s) may provide feasible processes to explain how hyperphalangy develops (Fig. 7B). It seems probable that reduced interdigital cell death found in flipper limbs could result from reduced BMP levels, increased BMP antagonism, reduced *msx-2* expression or some combination(s) of the above. Furthermore, extreme digit elongation found in hyperphalangeous digits of cetaceans would require prolonged expression of FGF-8 signals from the AER above the digits, suggesting increases in BMP antagonists (e.g. Gremlin, Noggin) mediated by hedgehog signalling, and preventing BMP regression of the AER. With maintenance of the interdigital cells and prolonged AER signalling, the digit specification pathway remains viable to provide the patterning mechanisms (BMPs and antagonists) for formation of additional phalanges.

### Hyperphalangy hypotheses

Howell (1970, reprint of 1930) provided a thorough summary of historical hypotheses for the development of hyperphalangy, while proposing his own explanation. Howell suggested that extra phalanges are added distally, in a stepwise manner after three phalanges (the plesiomorphic condition) differentiate within the autopod. Howell believed this theory for hyperphalangy was the 'only one yet advanced to which the known embryological evidence supplies any confirmation' (p. 266).

Both continuation of the AER for limb outgrowth and maintenance of pattern formation mechanism(s) have been identified as important factors for generation of hyperphalangy (Holder, 1983b). Holder's observation that factors affecting pattern formation must remain

operational suggests maintenance of the interdigital mesoderm is of importance based on our current understanding of digit joint patterning. Caldwell (1997a) proposed that explanations of hyperphalangy and elongation of the manus/pes involved 'peramorphic development during chondrogenesis (e.g., additional segmentation of chondrogenetic foci producing additional phalanges and enlargement of the metapodium)' (p. 306). The progress zone model and the maintenance of the AER during cetacean limb development were again highlighted by Richardson & Oeschläger (2002).

Although Richardson & Chipman (2003) claimed hyperphalangy does not correlate with a flipper autopod, they cite the example of the genus, *Chitra*, which has only a limited phalangeal increase, and an extensively webbed foot. In all known cases of extreme hyperphalangy represented here as exceeding the threshold value 4/6/6/6/6, the adult autopod has a flipper morphology. Based on this definition, hyperphalangy occurs only among secondarily aquatic vertebrates that have a flipper autopod.

As interdigital mesoderm plays an important role in joint induction and patterning, prevention of interdigital cell death appears to be a prerequisite for development of hyperphalangy; the signals must remain present for additional joint formation. However, it is also possible that the two extreme morphologies (flipper and hyperphalangy) coincidentally result from a single change in digit pathway (Fig. 7), such as increases in BMP antagonism that reduce interdigital cell death and provide joint patterning signals. Thus, although hyperphalangeous digits only occur in flipper limbs, the relationship may be coincidental; a causal relationship is not yet demonstrated, and not all flipper limbs demonstrate hyperphalangy.

However, increased BMP antagonism could reduce interdigital cell death, promote digit elongation and provide additional phalangeal patterning (Fig. 7A,C). Thus, development of hyperphalangy could result from an increase in BMP antagonism during the final stages of limb development, prolonging FGF expression (digit elongation) and joint patterning processes.

Future research on cetacean limb development may provide additional characterization of the spatial and temporal distribution of BMPs, BMP antagonists and FGF-8 expression in cetacean limbs and therefore provide opportunities to refine further the models of limb development based mainly on terrestrial model

organisms. It would be specifically interesting to determine if FGF-8 expression is maintained above the central digits of cetacean autopods, if interdigital BMP levels are reduced in cetacean limbs, or alternatively if expression of BMP antagonists is increased in comparison with terrestrial autopods.

## Polyphalangy

As with hyperphalangy, polyphalangy is found in taxa with a flipper-limb morphology. Some experimental evidence suggests a link to BMP within interdigital mesoderm. The experimental duplication of digit II (very early bifurcation of digit II anlagen?) and bifurcation of digit III by the application of ectopic BMP-2 to the anterior limb (Duprez et al. 1996) suggest that BMP-2 might play an important role in the development of polyphalangy.

Kleinenberg et al. (1969) found ten cases of polyphalangy (what they termed 'branched digits') among a survey of 105 adult Beluga whales, *Delphinapterus leucas*. The branching usually occurs bilaterally, but the pattern is variable and asymmetrical between each autopod. Beluga from different regions (populations) also showed tendencies for polyphalangy to occur on different digits. Kleinenberg et al. suggest that polyphalangy is a 'new development' that probably functions in strengthening the posterior portion of the flipper, typically occurring in digits IV and V.

Examination of Beluga embryonic material would offer a unique opportunity to examine the relationship between polyphalangy and the localized presence of factors such as BMP-2. It is hypothesized that elevated levels of BMP-2 or reduced BMP antagonism would be found in areas of the limb that demonstrate polyphalangy. In addition, it would be interesting to document any role FGF-8 expression patterns have on the development of polyphalangy, specifically whether branching occurs from a wider digit receiving multiple FGF-8 signals (Fig. 7C). The study of factors involved in the development of polyphalangy could provide data to evaluate further the debate regarding branching events (Shubin & Alberch, 1986; Cohn et al. 2002) and to help better understand malformations during limb development (Meteyer, 2000).

As mentioned previously, supernumerary digits of ichthyosaurs have been interpreted as developing via bifurcation of digital anlagen during elongation. Therefore, 'supernumerary digits' of ichthyosaurs might

also be attributed to increased levels of BMP in the interdigital mesoderm.

## Conclusions

It is important to clarify the ontogenetic stage being sampled (embryonic vs. adult morphologies) and whether ossification is a prerequisite for identification and counting of phalanges. Previous reports that cetacean embryos have more phalanges than adults are based on including cartilaginous elements, which are difficult to count accurately in flippers from adults, and impossible to identify in the fossil record.

Extreme hyperphalangy is limited to taxa with flipper autopods living in aquatic habitats. The absence of extreme hyperphalangy in any terrestrial taxa suggests there may be a (mechanical) constraint for this morphology. Hyperphalangy is found exclusively in the central digits, and has evolved multiple times among extant cetaceans. Additions of a single phalanx in some terrestrial taxa seem limited to the peripheral digits; however, terrestrial digits never exceed six phalanges.

Alterations of the limb-patterning pathway provide mechanisms for the production of hyperphalangy by reduction of interdigital mesodermal cell death (flipper limb), localized secondary maintenance of the AER (digit elongation) and induction of extra joints. Future work on cetacean limb development may provide the opportunity to refine what factors of the pathway are most likely to have been changed to produce this most interesting limb morphology. Cetacean limb development appears to provide an excellent model for understanding how hyperphalangy has developed in extinct fossil taxa such as Ichthyosaurs.

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