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New, puzzling insights from comparative myological studies on the old and unsolved forelimb/hindlimb enigma

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ABSTRACT

Most textbooks and research reports state that the structures of the tetrapod forelimbs and hindlimbs are serial homologues. From this view, the main challenge of evolutionary biologists is not to explain the similarity between tetrapod limbs, but instead to explain why and how they have diverged. However, these statements seem to be related to a confusion between the serial homology of the vertebrate pelvic and pectoral appendages as a whole, and the serial homology of the specific soft- and hard-tissue structures of the tetrapod forelimbs and hindlimbs, leading to an even more crucial and puzzling question being overlooked: why are the skeletal and particularly the muscle structures of the forelimb and hindlimb actually so strikingly similar to each other? Herein we provide an updated discussion of these questions and test two main hypotheses: (i) that the similarity of the limb muscles is due to serial homology; and (ii) that tetrapods that use hindlimbs for a largely exclusive function (e.g. bipedalism in humans) exhibit fewer cases of similarity between forelimbs and hindlimbs than do quadrupedal species. Our review shows that of the 23 arm, forearm and hand muscles/muscle groups of salamanders, 18 (78%) have clear ‘topological equivalents’ in the hindlimb; in lizards, 14/24 (58%); in rats, 14/35 (40%); and in modern humans, 19/37 (51%). These numbers seem to support the idea that there is a plesiomorphic similarity and subsequent evolutionary divergence, but this tendency actually only applies to the three former quadrupedal taxa. Moreover, if one takes into account the total number of ‘correspondences’, one comes to a surprising and puzzling conclusion: in modern humans the number of forelimb muscles/muscle groups with clear ‘equivalents’ in the hindlimb (19) is substantially higher than in quadrupedal mammals such as rats (14), lizards (14) and even salamanders (18). These data contradict the hypothesis that divergent functions lead to divergent morphological structures. Furthermore, as we show that at least five of the 19 modern human adult forelimb elements that have a clear hindlimb ‘equivalent’ derive from embryonic anlagen that are very different from the ones giving rise to their adult hindlimb ‘equivalents’, they also contradict the hypothesis that the similarity in muscle structures between the forelimb and hindlimb of tetrapods such as modern humans are due to their origin as serial homologues. This similarity is instead the result of phylogenetically independent evolutionary changes leading to a parallelism/convergence due to: (i) developmental constraints, i.e. similar molecular mechanisms are involved (particularly in the formation of the neomorphic hand), but this does not necessarily mean that similar anlagen are used to form the similar adult structures; (ii) functional constraints, related to similar adaptations; (iii) topological constraints, i.e. limited physical possibilities; and even (iv) phylogenetic constraints, which tend to prevent/decrease the occurrence of new homoplastic similarities, but also help to keep older, ancestral homoplastic resemblances.

Key words: analogy, comparative anatomy, evolution, development, limbs, muscles, pectoral, pelvic, serial homology, tetrapods.

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I. INTRODUCTION

It is commonly stated in the literature that the forelimb and hindlimb structures of tetrapods are serial homologues (e.g. Owen, 1866; Humphry, 1872*b*; Quain *et al.*, 1894; Abbasi, 2011). Historically, searching for serial homology in the body of humans and other vertebrates has its roots in the notion that all vertebrates originated from an ideal, simple, segmented ‘body ground-plan’ (the ‘archetype’), which could help to explain the configuration of all body parts and their individual structures (e.g. Owen, 1866). A clear example of this tradition is the influential paper of Humphry (1872*b*), which not only defended a strict serial homology between the forelimb and hindlimb muscles, but actually took this notion of ideal segmentation and symmetry to the extreme, proposing serial homologies between other body elements such as the constrictor oris (a constrictor of the mouth) and the sphincter ani externus (a constrictor of the anal canal and orifice). While this might seem to be simply a curious anecdote, it does reflect the human bias to seek for a simple ‘plan/pattern/trend’ that might help to simplify the complexity of animal form (Gould, 2002; see also Diogo & Wood, 2012). Although only a few researchers would nowadays accept serial homology between the constrictor oris and the sphincter ani externus and extreme views such as that of Humphry (1872*b*), instances are often seen, particularly in molecular developmental studies, where researchers state that the structures of the forelimb are serially homologous to those of the hindlimb (e.g. Ruvinsky & Gibson-Brown, 2000; Young & Hallgrímsson, 2005; Abbasi, 2011; Weisbecker, 2011; and references herein).

We do not wish to undervalue these studies as they are very important for understanding these issues, but we would like to stress that the idea of serial homology between the structures of the forelimbs and hindlimbs is currently accepted and that, based on this assumption, evolutionary and developmental biologists often state that the main challenge is to explain why there are significant differences between these limbs despite this serial homology. However, in our opinion such statements seem to be the result of confusion between different levels of taxonomic hierarchy, i.e. in considering that the serial homology of pelvic and pectoral appendages which occurred at some point in early vertebrate evolution could explain the similarity of specific soft and hard tissue-structures of the tetrapod limbs which originated much

later. In our view, this confusion has led, particularly in the last decades, to the overlooking of a crucial and puzzling question: why are the skeletal and particularly the muscle structures of the forelimb and hindlimb actually so strikingly similar to each other?

This confusion and particularly the failure to address this question and explain this striking similarity in a satisfactory scientific way created the opportunity for speculation and for harsh criticisms of evolutionary biology, mainly by creationists that argue that this is a clear example of an unsolvable paradox for evolutionary biologists. These creationists argue that it is not proposed in evolutionist literature that fore- and hindlimbs descended from a ‘common limb’, i.e. that there was never a tetrapod or a tetrapod ancestor with four exactly identical limbs, so according to them it is impossible to explain in an evolutionary context why the hard and soft-tissue structures of the hindlimbs and forelimbs are so similar (e.g. Denton, 1985). None of the authors of the present paper subscribes to such creationist views, however we think that it is remarkable, and important for the purpose of this paper, to see that some creationists are more aware of such a crucial evolutionary question than many evolutionary and developmental biologists.

An illustrative example of a scientific paper defending the idea of serial homology is that of Ruvinsky & Gibson-Brown (2000) in which it is stated that ‘similarities in their *bone* patterns reveal that forelimbs are homologous to hindlimbs, a phenomenon referred to as serial homology’ (p. 5233). In our opinion, this statement illustrates two major problems often seen in discussions about these topics: (i) serial homology is mainly suggested due to overall similarity, following the Owensian notion of ‘correspondence’ and not the currently accepted phylogenetic definition of serial homology (common origin) (Nixon & Carpenter, 2011; see below, on this Section); (ii) most current authors refer mainly to, are focused on, and only know in detail, what happens with skeletal structures, and not muscles and other soft tissues.

The hard tissues of the tetrapod limbs have been the subject of innumerable studies by developmental and evolutionary biologists, but unfortunately much less is effectively known about the soft tissues (Cole *et al.*, 2011). For example, in a recent and excellent book dedicated to discussing the transformation from fins to limbs (Hall, 2007), there is no mention of muscles. This biased effort towards the study of

hard tissues could also be due to the fact that soft tissue patterning seems to be much more complex than skeletal tissue patterning. As a consequence, there exist elegant models to explain skeletal tissue patterning of the limb [e.g. Shubin & Alberch (1986); see also, e.g. Fabrezi, Abdala & Oliver (2007) and Franssen *et al.* (2005) for variations of Shubin & Alberch's (1986) model; other alternative models have also been proposed, see e.g. Cohn *et al.* (2002) and Zhu *et al.* (2010)] whereas such a model has not yet been developed for limb musculature.

At this stage, and for the purpose of this paper, it is opportune to illustrate in some detail one of the many examples of striking, and deeply puzzling, similarity between the forelimb and hindlimb muscles, to provide the reader with an idea of the type of detail to which we are referring, i.e. we are not merely talking about the number of muscles in a certain region or the general, superficial configuration of the musculature of that region. The hand and foot muscles of our phylogenetically derived, bipedal species (*Homo sapiens*) provide such an example (Fig. 1) because in both the hand and foot there are: (i) superficial, short abductors of digits 1 (abductor hallucis/pollicis brevis) and of digits 5 (abductor digiti minimi) that attach on the base of the proximal phalanx of these digits; (ii) superficial flexors (flexor digitorum superficialis/flexor digitorum brevis) that attach onto the middle phalanges of digits 2–5 through bifurcated tendons; (iii) then, between these bifurcated tendons emerge the tendons of the long flexors (flexor digitorum profundus/longus) that insert onto the distal phalanges of digits 2–5; (iv) moreover, from these latter tendons originate four small muscles that attach onto both the base of the proximal and the extensor expansions of digits 2–5 (lumbricales); (v) additionally, there is a

separate long muscle that goes alone to the distal phalanx of digit 1 (flexor pollicis/hallucis longus) and that somewhat divides the so-called 'superficial/medial' and 'deep/lateral' heads of the flexor pollicis/hallucis brevis, which go to the base of the proximal phalanx of digit 1; (vi) on the other side of the autopodium, there is a flexor digiti minimi (brevis) going to the base of the proximal phalanx of digit 5; (vii) deep to these muscles, there is an adductor pollicis/hallucis that attaches to the proximal phalanx of digit 1 and that is divided into a transverse head and an oblique head; (viii) between the adductor pollicis/hallucis and the bones of digit 1 lies a short, thin muscle that usually inserts onto the base of the proximal phalanx of this digit ('volaris primus of Henle'/'interosseous plantaris hallucis'); (ix) lastly, deeper to the adductor pollicis/hallucis, there are three palmar/plantar interossei that insert onto the proximal phalanges of, and adduct the, digits, and four dorsal interossei that insert onto the proximal phalanges of, and abduct the, digits; (x) as an extravagant addition to these striking similarities, the pattern of innervation of all these hand and foot muscles is also remarkably similar, i.e. the short abductors and flexors of digit 1 and some lumbrical muscles are innervated by the median nerve (hand) and its 'equivalent' in the foot (medial plantar nerve), and all the other listed muscles by the deep branch of the ulnar nerve (hand) and its 'equivalent' in the foot (lateral plantar nerve), with no known exception to this pattern.

For some reason, such remarkable muscular similarities, which are well known to physicians and medical students, are often not acknowledged or at least not taken into account in current discussions about the evolution and/or development of the limbs. If they were, it would be clear that before addressing the question of why there are differences

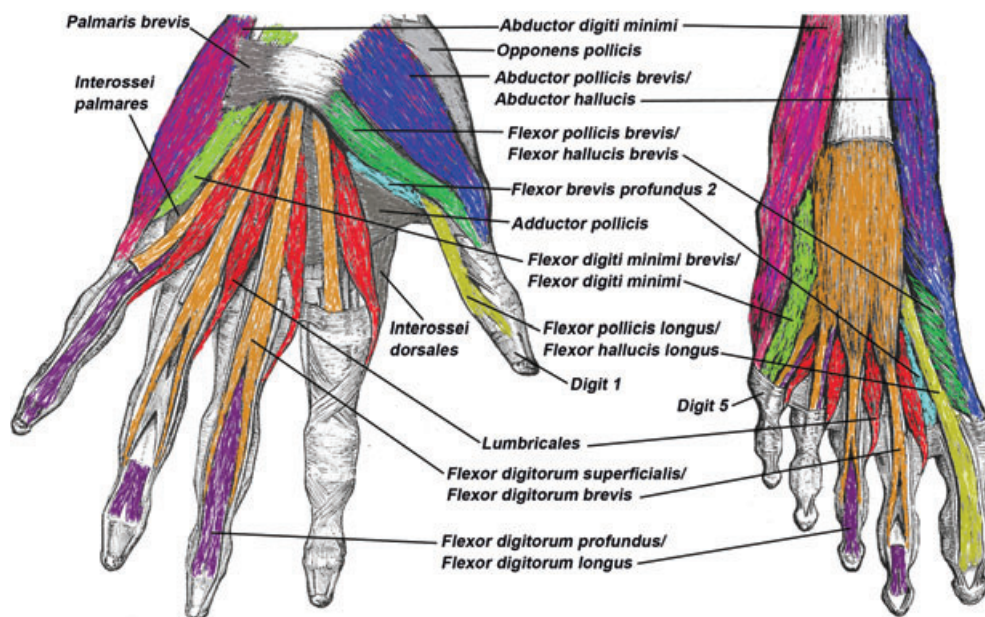


Fig. 1. Superficial musculature of the hand seen in palmar view (on the left) and of the foot seen in plantar view (on the right), showing the striking similarities between the muscles of the autopodium of the forelimb and hindlimb in modern humans (modified from Gray & Carter, 1858).

between the hind- and forelimb one needs first to address the more fundamental question of why there are such puzzling similarities. That is, discussing if these tissues are, or are not, serial homologues is not a merely semantic detail: it is instead something that is crucial in order to clarify which questions need to be addressed and which evolutionary/developmental analyses need to be undertaken in order to elucidate the old forelimb/hindlimb enigma.

In the present work we provide an updated discussion of the issues mentioned above and, based on extensive data obtained recently from representative taxa of all the major groups of vertebrates as well as on a literature review (comparative anatomy, evolutionary biology, developmental biology, molecular biology, genetics, and palaeontology), we test the hypothesis that the similarity between tetrapod fore- and hindlimb muscles is due to serial homology. As explained in the recent review of Nixon & Carpenter (2011, pp. 8–9), serial homology is identical to homology in the sense that both necessarily refer to ‘similarity due to an ancestral condition’. As they note, researchers often confuse the ‘Owensian ontogenetic definition of homology’ which ‘is devoid of phylogenetic content and is operational’ (basically meaning ‘correspondence’ and being, in fact, merely a hypothesis of homology, not true homology), with the term homology as currently defined under the cladistic paradigm, which ‘explicitly invokes an evolutionary (phylogenetic) context for similarity’. So, if there is true serial homology between the tetrapod hind- and forelimb muscles, it is expected that the muscles of phylogenetically plesiomorphic tetrapods such as salamanders will be more similar to each other than are the muscles of phylogenetically derived mammals such as modern humans (i.e. original, plesiomorphic similarity followed by evolutionary divergence). If there are no serial homologies but instead cases of analogous, phylogenetically independent evolution, it is expected that unavoidable cases of evolutionary divergence are significantly counterbalanced by obvious cases of evolutionary parallelism/convergence, leading to a substantial number of derived similarities that were not present plesiomorphically in tetrapods (e.g. due to ontogenetic, functional and/or topological constraints: see below, Section V). In addition, we test another hypothesis that is often proposed in the literature and that is related to the first hypothesis: that tetrapods that use hindlimbs for a largely exclusive function (e.g. bipedalism in humans) exhibit fewer cases of similarity between the forelimbs and hindlimbs than do quadruped species (see, e.g. Young & Hallgrímsson, 2005).

II. A NEW COMPARATIVE INSIGHT ON THE FORELIMB *VERSUS* HINDLIMB MUSCLES OF SALAMANDERS, LIZARDS, RATS AND MODERN HUMANS

Most studies on the evolution of tetrapods and other vertebrates have been based on hard tissue data. To address the paucity of data on soft tissues such as muscles, R. Diogo

and colleagues recently reported results of a long-term study of the comparative anatomy, homologies and evolution of the muscles of all major groups of non-primate vertebrates and of primates based on dissection of hundreds of specimens and on an extensive review of the literature (e.g. Diogo *et al.*, 2008, 2009a, b, 2010; Diogo & Abdala, 2010; Diogo & Wood, 2011, 2012). Herein, we use our knowledge of the comparative anatomy of vertebrate muscles to provide a new comparative insight on the forelimb *versus* hindlimb of tetrapods. In Tables 1–4 we compare these muscles in the following key taxa that were carefully chosen from the many tetrapod taxa we have dissected in the past: the amphibian salamander *Ambystoma mexicanum*, the reptilian lizard *Timon lepidus*, the mammalian rodent *Rattus norvegicus*, and modern humans (*Homo sapiens*). The Norwegian rat was chosen because rats are often considered as ‘anatomically generalized’ therian mammals, but at the same time are somewhat closely related to primates (both groups are included in the clade Euarchontoglires).

Different authors often disagree about homologies between muscles of the same anatomical region (e.g. the head or the hand) in different taxa (Diogo & Abdala, 2010). It is even more difficult to agree about ‘topological correspondence’ [as defined by Owen (1866), see above] between muscles such as those of the hindlimb and those of the forelimb. For the present study we opted to use, in a systematic way, the most simple, conservative and thus least subjective and least biased method to compare these muscles in Tables 1–4. That is, for each taxon, we simply counted the number of individual muscles/muscle groups of the hindlimb that clearly seem to ‘correspond’ topologically to individual muscles/muscle groups of the forelimb, i.e. we only counted those ‘correspondences’ that can be easily discriminated by any researcher/student with minimal training in comparative anatomy (e.g. by medical students). We used the criteria that have been used historically to search for the ‘correspondence’ between body parts of an organism, i.e. ‘positional or topographical similarity’ *sensu* Owen (1866; see also Nixon & Carpenter, 2011) or ‘morphological congruence’ *sensu* Shubin & Alberch (1986). That is, both R. D. and V. A. analysed each muscle (distal attachments, proximal attachments, number of divisions, relations to other hard and soft-tissue structures, orientation of fibres, and number of crossed joints) in order to investigate independently which forelimb muscle elements of the taxa listed in Tables 1–4 have a clear, direct (one to one) topological ‘equivalent’ in the hindlimb of the same taxa. For this specific phase of our project we intentionally did not take into consideration other types of data that were not topological and that could suggest more ‘speculative/overdone’ and/or ‘obscure/less apparent’ cases of ‘correspondence’ (e.g. ontogeny of wildtype animals, development of transgenic animals, gene expression; we refer to and discuss those other types of data in relevant sections below). In the next phase of the project both R. D. and V. A. compared the results obtained by each other in order to identify the cases in which there was agreement; the results of this comparison are shown in Tables 1–4

Table 1. Scheme illustrating hypotheses regarding the homologies of the arm muscles of adults of representative tetrapod taxa (adapted from Diogo & Abdala, 2010)

<i>Ambystoma mexicanum</i> [three arm muscles/muscle groups: 0 (0%), seem to 'correspond' directly to thigh muscles/muscle groups ¹]	<i>Timon lepidus</i> [four arm muscles/muscle groups: 0 (0%) seem to 'correspond' directly to thigh muscles/muscle groups ²]	<i>Rattus norvegicus</i> [five arm muscles/muscle groups: 0 (0%), seem to 'correspond' directly to thigh muscles/muscle groups ³]	<i>Homo sapiens</i> [four arm muscles/muscle groups: 0 (0%), seem to 'correspond' directly to thigh muscles/muscle groups ⁴]
Triceps brachii	Triceps brachii	Triceps brachii	Triceps brachii
—	—	Dorsoepitrochlearis (might derive instead from latissimus dorsi)	—
Humeroantibrachialis	Brachialis	Brachialis	Brachialis
—	Biceps brachii	Biceps brachii	Biceps brachii
Coracobrachialis	Coracobrachialis	Coracobrachialis	Coracobrachialis

Data compiled from evidence provided by our own dissections and comparisons, and from a review of the literature. The black arrows indicate hypotheses that are most strongly supported by the evidence available; the grey arrows indicate alternative hypotheses that are supported by some data, but that overall are not as strongly supported by the evidence as are the hypotheses indicated by the black arrows. In Tables 2–4, below the names of those forelimb muscles/muscle groups that have clear, direct topological hindlimb 'equivalents' in the same taxon, we provide (in bold, between square brackets) the names of those hindlimb 'equivalents'. In those cases in which those 'equivalents' clearly have a different ontogeny, these are shown in bold and italics. For further details, see text, Tables 2–4.

¹The triceps brachii of urodeles usually includes coracoideus ('coracotriceps'), scapularis medialis ('dorsitriceps'), humeralis lateralis ('humerotriceps lateralis') and humeralis medialis ('humerotriceps lateralis') sections, which correspond respectively to the 'anconeus coracoideus', 'anconeus scapularis medialis', 'anconeus humeralis lateralis' and 'anconeus humeralis medialis' *sensu* Walthall & Ashley-Ross (2006). Howell (1935, 1937) suggests that the 'coracotriceps' of urodeles might correspond to the triceps coracoideus of reptiles such as *Iguana* and thus to the dorso-epitrochlearis of mammals. The overall configuration of the triceps brachii of salamanders is very different from that of the structure that is sometimes named 'quadriceps femoris' in salamanders, which usually includes a rectus femoris (that corresponds to part or the totality of the muscle that is often designated as 'iliotibialis', and/or to the 'ilioextensorius' *sensu* Kardong, 2002) but does not include three differentiated musculi vasti such as those often seen in mammals (e.g. Ashley-Ross *et al.*, 1991; Ashley-Ross, 1992). *Ambystoma mexicanum* and various other salamanders only have a single flexor of the forearm, the humeroantibrachialis, while they have various flexors of the leg, e.g. the 'iliofibularis', the 'femorofibularis' and the 'ischioflexorius' *sensu* Ashley-Ross *et al.* (1991) and Ashley-Ross (1992).

²According to Holmes (1977) and Dilkes (2000) the number of heads of the triceps brachii is usually four ('scapular', 'coracoid', 'lateral humeral', and 'medial humeral') in lepidosaurs, including *Sphenodon*. Holmes (1977) argues that having four heads is the plesiomorphic condition for reptiles, and Diogo & Abdala (2010) support the idea that this is also the plesiomorphic condition for amniotes and for extant tetrapods as a whole, because extant amphibians often have four heads of the triceps brachii and mammals usually have three heads of the triceps plus a dorsoepitrochlearis muscle that likely derives from/corresponds to the coracoid head of the triceps of other tetrapods. However, the overall configuration of the triceps brachii of lizards is not similar to the so-called 'quadriceps femoris' of these lepidosaurs, which actually usually does not include four heads, i.e. it includes a rectus femoris (that in lepidosaurs is often designated as 'iliotibialis'), as well as 'musculi vasti' (that in lepidosaurs is often designated as 'femorotibialis'), but the configuration of these latter muscles is variable and there are no distinct, well-separated vastus medialis, vastus intermedius and vastus lateralis in lepidosaurs as is often the case in mammals (see, e.g. Ellsworth, 1972; Dilkes, 2000; Russell & Bauer, 2008). Regarding the flexors in the arm and thigh, there is only one flexor in the arm crossing two joints (biceps brachii) while there are at least three flexors in the thigh that often cross two joints (the semimembranosus, semitendinosus and biceps femoris, which are often named respectively 'flexor tibialis internus', 'flexor tibialis externus' and 'iliofibularis' in reptiles); moreover there is also no clear 'equivalent' of the brachialis, because no flexor in the thigh runs from the femur to the leg (see, e.g. Ellsworth, 1972).

³In some non-human primates and at least some tree-shrews the triceps brachii has four heads, and this could be a further argument that the triceps brachii 'corresponds' to the quadriceps femoris; however, in *Rattus norvegicus* the triceps brachii has three heads, as does the triceps brachii of modern humans, so in *R. norvegicus* there is also no direct 'correspondence' between this muscle and the quadriceps femoris. In addition to the four arm muscles found in modern humans, *R. norvegicus* (as well as most non-human primates and most other mammals) has a dorsoepitrochlearis, which has been said to 'correspond' to the sartorius (e.g. Quain *et al.*, 1894). However, in *R. norvegicus* the sartorius is usually not present as a distinct muscle (e.g. Greene, 1935) and, moreover, the dorsoepitrochlearis of mammals actually probably corresponds to one of the four heads that usually form the triceps brachii of other tetrapods; Ellsworth (1972) suggests that the mammalian sartorius might be simply an extension of the psoas. In rats the biceps femoris is often divided into anterior, posterior and accessory heads, so there are often five flexor structures in the thigh crossing two joints (these three heads, the semimembranosus and the semitendinosus), while there are only two flexor structures in the arm crossing two joints (the two heads of the biceps brachii) (e.g. Greene, 1935; Walker & Homberger, 1997). However, rats, as well as various other mammals, have a caudofemoralis muscle in the thigh that might 'correspond' to the coracobrachialis of the arm, because: (i) the caudofemoralis of rats is said to be a hamstring muscle that is associated, and often partially blended, with other hamstring muscles such as the semimembranosus (e.g. Greene, 1935; Ellsworth, 1972; N.B., the coracobrachialis is often associated and partially blended with the biceps brachii); (ii) the innervation of the caudofemoralis of rats is by the tibial division of the sciatic nerve, as is the innervation of other hamstring muscles such as the semimembranosus (e.g. Greene, 1935; N.B. both the coracobrachialis and the biceps brachii, as well as the brachialis, are mainly innervated by the same nerve, the musculocutaneous); and (iii) the caudofemoralis of rats usually runs from sacral/caudal vertebrae to the femur, thus crossing only the most proximal—hip—joint of the hindlimb (e.g. Greene, 1935; N.B., the coracobrachialis usually runs from the scapula to the humerus, thus crossing only the most proximal—shoulder—joint of the forelimb). These fine details could thus support a possible 'correspondence' between the caudofemoralis and the coracobrachialis, but the reality is that in a gross anatomical comparison of these two muscles their overall configuration and topology are not similar and to our knowledge no previous authors have consistently supported such a 'correspondence'; such 'correspondence' is even less apparent in other, non-mammalian tetrapods, in which the caudofemoralis is more associated with the movements of the tail, being often designated as 'agitador caudae' or as 'femorococcygeus', 'femorocaudalis', or 'caudi-femoralis': see, e.g. Ellsworth (1972).

⁴Based mainly on comparative anatomy, it has been suggested that in modern humans at least some of the muscles of the thigh correspond to some of the muscles of the arm, e.g. that the ischial head of the biceps femoris plus the semitendinosus plus the semimembranosus might correspond to at least part of the biceps brachii, that the femoral head of the biceps femoris might correspond to the brachialis, and that the quadriceps femoris might correspond to the triceps brachii (e.g. Quain *et al.*, 1894). However, there is no clear, direct ‘correspondence’ between any arm and thigh muscles. For instance, the biceps brachii has two heads while the biceps femoris plus the semitendinosus plus the semimembranosus form four structures in total [one could also consider the coracobrachialis, but contrary to any of these three latter thigh muscles the coracobrachialis only crosses one—the shoulder—joint; according to authors such as Quain *et al.* (1894) the coracobrachialis ‘corresponds’ to at least two or more gluteal muscles, i.e. the obturator internus, obturator externus, gemellus superior, gemellus inferior, quadratus femoris and/or part of the adductor magnus. Also, the triceps brachii has three heads while the quadriceps femoris has four heads. The brachialis runs from the humerus to the ulna, and the short head of the biceps femoris runs from the femur to the fibula, but the former muscle is clearly separate from the other flexor muscles in the arm, while the latter head is clearly associated and inserts together, through the same tendon, with the long head of the biceps femoris. We are not stating that these arm and thigh structures do not have any resemblance, as there are some similarities between the long head of the triceps crossing two joints and the rectus femoris part of the quadriceps femoris also crossing two joints, and between the brachialis crossing one joint to attach onto the ulna and the short head of the biceps femoris crossing one joint to attach onto the fibula. We are simply stating that for the purposes herein, and following the methodology outlined in Section II, there is no clear, direct ‘correspondence’ between any of the individual muscles of the arm and of the thigh.

(see also example in Fig. 2). Of course, different researchers could opt to follow other methods than those used here; e.g. they could argue that one should look for the maximum number of ‘correspondences’ instead and thus also include those less apparent/more speculative cases as well. But the important point here is that by systematically performing an independent verification to search explicitly for the minimum number of clear, direct ‘correspondences’ in each of the four taxa, we ensure that the results for each taxon can be compared systematically in a meaningful way.

An illustrative example of how we apply this methodology concerns the forearm muscle extensor antebrachii et carpi radialis and the leg muscle tibialis anterior. Numerous authors have pointed out that these muscles ‘correspond’ topologically to each other (e.g. Humphry, 1872*b*; Quain *et al.*, 1894), and our dissections clearly support this idea (see Table 3). Therefore, in Table 3 the extensor antebrachii et carpi radialis of lizards is shown as having a clear, muscle-to-muscle ‘correspondence’ with the tibialis anterior. However, as explained below and shown in Table 3, in adult mice there are two ‘extensor carpi radialis’ muscles, the extensor carpi radialis longus and the extensor carpi radialis brevis, so there is no direct muscle to muscle ‘correspondence’ between the tibialis anterior and any individual muscle of the forearm. This is precisely the type of data we want to obtain, compare and discuss in order to test the hypotheses of evolutionary divergence leading to different structures *versus* evolutionary parallelism/convergence leading to similar structures, as outlined in Section I.

In the comparisons provided in Tables 1–4 and in the text, the nomenclature for the pectoral and forelimb muscles follows that of Diogo & Abdala (2010), while that of the pelvic and hindlimb muscles mainly follows that used in the recent musculoskeletal atlases published by R. Diogo and colleagues (e.g. Diogo *et al.*, 2010). Apart from the taxa listed in Tables 1–4, we have dissected hundreds of specimens from all the major groups of vertebrates; a list of the dissected non-primate vertebrate specimens is given in Diogo & Abdala (2010), while a list of the dissected primates is given in Diogo & Wood (2012).

III. FORELIMB AND HINDLIMB MUSCLES: SIMILARITIES, DIFFERENCES AND HOMOPLASIES

Under the ‘original plesiomorphy subsequent evolutionary divergence’ scenario it would be expected that the paired appendages of early paired-fins animals presented higher morphological similarity than in more derived animals and that this divergence occurred concomitantly to changes in functional demands. However there is evidence that contradicts this viewpoint. King *et al.* (2012) have shown that a species of African lungfish (Sarcopterygii: *Protopterus annectens*) uses a range of pelvic-fin-driven, tetrapod-like gaits, including walking and bounding, in an aquatic environment. This and other works have shown that various morphological characteristics of tetrapod limb anatomy evolved in an aquatic environment quite independently of their later usefulness for terrestrial locomotion during the rise of tetrapods. That is, these morphological characteristics represent not adaptations but exaptations to terrestrial locomotion.

On the other hand, these and other studies clearly show that in at least some lungfish, and very likely also in plesiomorphic tetrapods, there were crucial differences in the function of the pectoral and pelvic appendages. So, the forelimb and hindlimb of tetrapods arose from sarcopterygian appendages (pectoral and pelvic) that were most likely very different from each other (in extant sarcopterygian fish they are usually very different, particularly their girdles: e.g. see fig. 2.3 in Coates & Ruta, 2007) and that were, moreover, essentially evolving to perform different functions (i.e., in a gait that is essentially pelvic fin/hindlimb-driven, and a type of locomotion that is much less axially powered than in plesiomorphic fish where the tail plays a more important locomotory role).

Some authors state that despite this morphological disparity between the pelvic and pectoral appendages of paired-fin organisms, these appendages are serially homologous at the molecular level. Ruvinsky & Gibson-Brown (2000) stated that there are two main models to account for the evolution of vertebrate limbs at a

Table 2. Scheme illustrating hypotheses regarding the homologies of the ventral forearm muscles of adults of representative tetrapod taxa (adapted from Diogo & Abdala, 2010; see legend to Table 1 for further details)

<i>Ambystoma mexicanum</i> [nine ventral forearm muscles/muscle groups: 7 (78%), seem to 'correspond' directly to leg muscles/muscle groups ¹]	<i>Timon lepidus</i> [eight ventral forearm muscles/muscle groups: 5 (63%) seem to 'correspond' directly to leg muscles/muscle groups ²]	<i>Rattus norvegicus</i> [eight ventral forearm muscles/muscle groups: 5 (63%), seem to 'correspond' directly to leg muscles/muscle groups ³]	<i>Homo sapiens</i> [eight ventral forearm muscles/muscle groups: 6 (75%), seem to 'correspond' directly to leg muscles/muscle groups ⁴]
Palmaris profundus 1 [Pronator profundus]	—	—	—
Pronator quadratus [Interosseous cruris]	Pronator quadratus [Interosseous cruris]	Pronator quadratus	Pronator quadratus
—	Pronator accessorius	—	—
Contraheptium caput longum [Caput longum musculorum contraheptium]	—	—	—
Flexor accessorius lateralis [Flexor accessorius lateralis]	—	—	—
Flexor accessorius medialis [Flexor accessorius medialis]	—	—	—
Flexor digitorum communis [Flexor primordialis communis]	Flexor digitorum longus [Flexor digitorum longus]	Flexor digitorum profundus [Flexor digitorum longus]	Flexor digitorum profundus [Flexor digitorum longus]
—	—	Flexor pollicis longus [Flexor hallucis longus]	Flexor pollicis longus [Flexor hallucis longus]
Flexores digitorum superficiales (hand muscles) [Flexores digitorum breves]	Flexores digitorum superficiales (hand muscles) [Flexores digitorum breves]	Flexor digitorum superficialis [Flexor digitorum brevis]	Flexor digitorum superficialis [Flexor digitorum brevis: ≠ ontogeny]
—	—	Palmaris longus [Plantaris]	Palmaris longus [Plantaris: ≠ ontogeny]
Flexor antebrachii et carpi ulnaris	Flexor carpi ulnaris	Flexor carpi ulnaris	Flexor carpi ulnaris
—	Epitrochleoanconeus	Epitrochleoanconeus	—
Flexor antebrachii et carpi radialis	Flexor carpi radialis [Tibialis posterior, i.e. 'pronator profundus']	Flexor carpi radialis [Tibialis posterior]	Flexor carpi radialis [Tibialis posterior]
—	Pronator teres [Popliteus]	Pronator teres [Popliteus]	Pronator teres [Popliteus]

¹As stressed by Walthall & Ashley-Ross (2006) the ventral muscles of the forearm and the posterior muscles of the leg of salamanders are remarkably similar. The leg muscle that these authors designated as 'pronator profundus' 'corresponds' to the forearm muscle that they designated by the same name, which is a derivative of the pronator quadratus and should actually be designated as palmaris profundus 1 because apart from this muscle *Ambystoma mexicanum* also has a separate pronator quadratus (e.g. Grim & Carlson, 1974; our dissections) that 'corresponds' to the leg muscle that Walthall & Ashley-Ross (2006) designated as interosseous cruris. In summary, the flexor antebrachii et carpi ulnaris and the flexor antebrachii et carpi radialis are the only ventral muscles of the forearm that have no clear 'equivalents' in the leg of salamanders.

²Lizards such as *Timon lepidus* usually do not have a distinct muscle palmaris longus (e.g. Diogo & Abdala, 2010) nor a distinct muscle plantaris (e.g. Dilkes, 2000; Kardong, 2002); according to Kardong (2002) the plantaris of mammals derives from part of the gastrocnemius of reptiles. They also do not have a distinct muscle tibialis posterior, i.e. the tibialis posterior of mammals probably corresponds to part of the gastrocnemius of these lizards (see, e.g. Russell, 1993; Russell & Bauer, 2008). As rats, they also do not have a distinct flexor pollicis longus, but have an epitrochleoanconeus, which does not have a clear, direct 'equivalent' in the leg (e.g. Diogo & Abdala, 2010). Although it is often stated in the literature that lizards and other reptiles do not have a tibialis posterior (e.g. Kardong, 2002), previous authors such as Owen (1866) have defended that the leg muscle that is often designated as 'pronator profundus' in lizards (see, e.g. Russell, 1993) does correspond to the tibialis posterior of mammals, and have thus designated the lizard leg muscle as 'tibialis posticus'. In the monograph based on his comprehensive analysis of the hand and foot muscles, Lewis (1989) also defends this idea, stating that lizards do usually have a tibialis posterior, which originates from the fibula and is often designated as 'profundus'. Our observations and comparisons also support this idea, because the lizard leg muscle usually originates from the fibula and runs somewhat distomedially in order to mainly attach onto the medial region of the tarsals/metatarsals (e.g. on metatarsal I), as usually does the tibialis posterior of mammals (see, e.g., fig. 10 of Russell, 1993). Moreover, this lizard leg muscle does not seem to 'correspond' to the arm muscle pronator quadratus, which is often named 'pronator profundus' and/or 'pronator accessorius' in the literature, because: (i) this latter muscle usually connects the two forearm bones (ulna to radius), and usually does not extend to the carpal/metacarpal region, and (ii) because reptiles, including lizards, do usually have a leg muscle that is designated 'interosseous cruris' and that does seem to 'correspond' to the pronator quadratus (and probably to its derivative, the pronator accessorius), connecting the two leg bones (fibula to tibia) (see, e.g., fig. 158 of Owen, 1866; Hutchinson, 2002). Therefore, the pronator accessorius is a peculiar muscle derived from the pronator quadratus that is only present in a few reptiles (e.g., Abdala & Diogo, 2010), and that does not seem to have a clear 'equivalent' in the leg of lizards (see, e.g. Russell, 1993; Russell & Bauer, 2008). The hand muscles flexores digitorum breves/superficiales, which seem to 'correspond' directly to the flexores digitorum breves of the foot, are shown in Table 2 because they contributed to the formation of mammalian forearm muscles such as the flexor digitorum superficialis (e.g. Diogo & Abdala, 2010).

³The considerations made for modern humans apply to rats, the only differences being that rats do not have a distinct muscle flexor pollicis longus (see text), have an epitrochleoanconeus (which is a small muscle running from the medial epicondyle of the humerus to the ulna that has no clear, direct 'equivalent' in the leg), and have some additional fibular muscles in the leg, e.g. the fibularis digiti quarti and fibularis digiti quinti, which do not have clear, direct 'equivalents' in the forearm (see, e.g. Greene, 1935; Diogo & Wood, 2012).

⁴Six ventral forearm muscles of modern humans clearly seem to 'correspond' directly with muscles found in the leg. Both the flexor digitorum profundus and the flexor digitorum longus run deep to the flexor digitorum superficialis and to the flexor digitorum brevis, respectively, passing between the distal tendons of these latter muscles in order to insert onto the distal phalanges of the digits 2–5, while the flexor pollicis longus and flexor hallucis longus attach onto the distal phalanges of the thumb and of the big toe, respectively. The palmaris longus and plantaris are superficial, thin muscles crossing the elbow/knee joints as well as the wrist/ankle joints to promote a weak flexion of the forearm/leg and of the hand/foot. Both the popliteus and the pronator teres run from the side of the hindlimb/forelimb where digit 1 is (from the medial epicondyle of the femur and the lateral condyle of the humerus, respectively) to the proximal region of the bone

that lies on the other side of the hindlimb/forelimb (of the tibia and radius, respectively). Lastly, both the tibialis posterior and the flexor carpi radialis insert onto the tarsal/metatarsal (or carpal/metacarpal) region that lies proximal to digit 1, not inserting onto the phalanges, thus promoting both a flexion and a movement of the hand/foot towards the side of digit 1 (i.e. the so-called ‘abduction’ of the hand and the so-called ‘inversion’ of the foot; the evident gross anatomical similarity of these two muscles has been confirmed in recent developmental and genetic studies of other taxa, see e.g. DeLaurier *et al.*, 2006). Therefore, the only two ventral forearm muscles that have no clear topological ‘equivalents’ in the leg are the pronator quadratus and the flexor carpi ulnaris. The insertion, function and innervation of the fibularis tertius are more similar to those of the extensor carpi ulnaris in the sense that the two muscles go to metatarsal/metacarpal V, promote both a dorsiflexion/extension of the foot/hand and a movement of the foot/hand towards the side of digit 5 (eversion of foot, adduction of hand), and are innervated by the same nerve that innervates the remaining extensors in the leg/forearm (i.e. deep fibular nerve and radial nerve, respectively). Also, the flexor carpi ulnaris is similar to the fibularis longus and particularly to the fibularis brevis in the sense that both the flexor carpi ulnaris and the fibularis brevis are at least partially inserted on metatarsal/metatarsal V, promote a flexion/plantarflexion plus a movement of the hand/foot towards the side of digit 5 (i.e. adduction of hand and eversion of foot), and are innervated by a nerve that does not innervate most of the other flexors in the forearm/leg [i.e. they are innervated respectively by the ulnar (rather than median) nerve, and by the superficial (rather than deep) fibular nerve]. However, previous authors have supported the idea that the extensor carpi ulnaris, and not the flexor carpi ulnaris, ‘corresponds’ to the fibularis longus plus fibularis brevis of the leg, the idea being that at some point in time these muscles probably dorsiflexed the foot (e.g. Humphry, 1872*a, b*; Quain *et al.*, 1894). Support for this idea mainly comes from developmental studies, which have shown that there are mainly three anlagen in the posterior leg: (i) a lateral anlage (similar to the forelimb anlage that gives rise to the flexor carpi ulnaris and epitrochleoanconeus) that seemingly gives rise to the soleus and gastrocnemius, which only become respectively attached to the tibia and the medial condyle of the femur later in ontogeny—the plantaris apparently derives from this anlage and specifically from the gastrocnemius; (ii) a central anlage (similar to the forelimb anlage that gives rise to the flexor digitorum longus and flexor pollicis longus and also to the proximal portions of the flexor digitorum superficialis and palmaris longus) that gives rise to the flexor digitorum longus and flexor hallucis longus; (iii) a medial anlage (similar to the forelimb anlage that gives rise to the flexor carpi radialis and to the pronator teres) that gives rise to the tibialis posterior and popliteus. There are also three anlagen in the anterior leg: (i) a lateral anlage (similar to the forelimb anlage that gives rise to the extensor carpi ulnaris and anconeus) that seemingly gives rise to the fibularis longus and fibularis brevis; (ii) a central anlage (similar to the forelimb anlage that gives rise to the extensor digitorum) that gives rise to the extensor digitorum longus and extensor hallucis longus; (iii) a medial anlage (similar to the forelimb anlage that gives rise to the extensor carpi radialis longus, extensor carpi radialis brevis, supinator and brachioradialis) that gives rise to the tibialis anterior. In this sense, the fibularis tertius could ‘correspond’ to the extensor digiti minimi, as suggested by Quain *et al.* (1894), because both these muscles go to digit 5. However, the fibularis tertius and extensor digiti minimi are topologically very different: the fibularis tertius is a very thin, small, apparently vestigial structure that is often reduced to a single tendon running from the extensor digitorum longus to metatarsal V, thus crossing the ankle joint and acting on the foot but not extending to the digits (nor crossing the elbow joint), while the extensor digiti minimi of modern humans is a well-developed muscle that has a fleshy belly originating from the common extensor tendon of the lateral epicondyle of the humerus and that has a tendon going to the extensor expansion of digit 5. It should be noted that the extensor digiti minimi is ontogenetically derived from the anlage of the extensores digitorum breves, while the fibularis tertius is seemingly derived from the anlage that gives rise to the extensor digitorum longus (e.g. Lewis, 1910; Cihak, 1972; Diogo & Wood, 2011, 2012).

molecular level: some researchers suggest that the pectoral fins evolved as a consequence of the rostral homeotic transposition of a pre-existing set of pelvic fins resulting from the novel redeployment of *Hox* genes; other authors suggest that the evolution of the positioning of paired appendages is the result of a co-option of a ‘*Hox* code’ that had originally evolved in splanchnic (gut) mesoderm to regulate rostrocaudal patterning of the digestive tract. Ruvinsky & Gibson-Brown (2000) state that the ‘fossil record’ suggests that the ‘morphology of the pelvic appendages is primitively (i.e. in fish) different from that of the pectoral pair’ (p. 5241), and subsequently formulate the question: ‘since the two sets of appendages are serially homologous, what mechanisms can account for the observed differences?’ Their answer is that one way in which distinct morphologies likely evolve in serially homologous structures can be proposed as an extension of Lewis & Wolpert’s (1976) notion of ‘positional nonequivalence’, which emphasizes the fundamental differences between cells located at different positions within the embryo (p. 5241). Thus, at the origin of paired appendages they would be serially homologous because they would develop from the same genetic regulatory network and different morphologies would be due to differences in the concentration of signaling molecules (‘positional nonequivalence’; Lewis & Wolpert,

1976). Later on, this common genetic regulatory network would diverge (due to mutations in the regulatory elements of developmental genes and also in gene sequences), and this would also lead to higher morphological divergence between paired appendages. According to Shubin *et al.* (1997) genetic systems must have provided, through the successive co-option and redeployment of molecular signals, a framework for the evolutionary integration of pectoral and pelvic appendages. Earliest vertebrate appendages (e.g. median fins) probably did not use *hox* genes; *HoxA* and *HoxD* genes are not expressed during the outgrowth of zebrafish median fins. Thus, there was a moment in evolution in which the development of paired appendages was brought under similar regulatory control (gene co-option), establishing serially homologous designs; e.g. digits arose at the same time in the hand and foot because there is no Devonian tetrapod with fingers and no toes. According to Shubin *et al.* (1997), polydactylous hands and feet have almost never been fixed in phylogeny, despite the presence of polydactylous variants within populations of various taxa; when nerves, bones and muscles of the limbs were formed, they had to follow the same pattern.

A study that provided crucial data for the understanding of both the similarities and the differences of the forelimb and hindlimb hard and soft-tissue structures is that of

Table 3. Scheme illustrating hypotheses regarding the homologies of the dorsal forearm muscles of adults of representative tetrapod taxa (adapted from Diogo & Abdala, 2010; see legend to Table 1 for further details)

<i>Ambystoma mexicanum</i> [six dorsal forearm muscles/muscle groups: 6 (100%), seem to 'correspond' directly to leg muscles/muscle groups ¹]	<i>Timon lepidus</i> [five dorsal forearm muscles/muscle groups: 48 (0%) seem to 'correspond' directly to leg muscles/muscle groups ²]	<i>Rattus norvegicus</i> [11 dorsal forearm muscles/muscle groups: 2 (18%), seem to 'correspond' directly to leg muscles/muscle groups ³]	<i>Homo sapiens</i> [12 dorsal forearm muscles/muscle groups: 3 (25%), seem to 'correspond' directly to leg muscles/muscle groups ⁴]
Extensor carpi radialis [Extensor tarsi tibialis]	Extensor antebrachii et carpi radialis [Tibialis anterior]	Extensor carpi radialis longus	Extensor carpi radialis longus
—	—	Extensor carpi radialis brevis	Extensor carpi radialis brevis
—	—	—	Brachioradialis
Supinator [Extensor cruris tibialis]	—	Supinator	Supinator
Extensor antebrachii et carpi ulnaris [Extensor cruris et tarsi fibularis]	Extensor antebrachii et carpi ulnaris	Extensor carpi ulnaris	Extensor carpi ulnaris
—	—	Anconeus	Anconeus
Extensor digitorum [Extensor digitorum communis]	Extensor digitorum [Extensor digitorum longus]	Extensor digitorum [Extensor digitorum longus]	Extensor digitorum [Extensor digitorum longus]
Extensores digitorum breves [Extensores digitorum breves]	Extensores digitorum breves [Extensores digitorum breves]	—	—
—	—	Extensor digiti minimi	Extensor digiti minimi
—	—	Extensor digiti quarti	—
—	—	Extensor indicis	Extensor indicis
—	—	Extensor pollicis longus [Extensor hallucis longus]	Extensor pollicis longus [Extensor hallucis longus: ≠ ontogeny]
Abductor et extensor digiti 1 [Abductor et extensor digiti 1]	Abductor pollicis longus [Extensor hallucis longus]	Abductor pollicis longus	Abductor pollicis longus
—	—	—	Extensor pollicis brevis [Extensor hallucis brevis: ≠ ontogeny]

¹As stressed by Walthall & Ashley-Ross (2006) the dorsal muscles of the forearm and the anterior muscles of the leg of salamanders are remarkably similar. As explained in Section II, the extensor antebrachii et carpi radialis of lizards has a clear 'correspondence' to the tibialis anterior, but in salamanders there are two muscles lying in the position of tibialis anterior of other tetrapods, i.e. the extensor cruris tibialis (seemingly 'corresponding' to an 'extensor antebrachii radialis' and thus to the supinator *sensu* the present work) and the extensor tarsi tibialis (seemingly 'corresponding' to the extensor carpi radialis) *sensu* Walthall & Ashley-Ross (2006). So in these amphibians the extensor carpi radialis and the supinator (both muscles are present in, e.g., *Ambystoma mexicanum*: e.g. Grim & Carlson, 1974; our dissections) have clear, direct muscle-to-muscle 'correspondence' to the two muscles of the leg.

²All the dorsal forearm muscles/muscle groups of lizards have a clear, direct 'equivalent' in the leg, with exception of the extensor antebrachii et carpi ulnaris (contrary to salamanders, where there is only one muscle in the leg—i.e., the extensor cruris et tarsi fibularis—that 'corresponds' topologically to the extensor antebrachii et carpi ulnaris of the forearm, in lizards there are often numerous muscles lying on the anterolateral region of the leg, including the fibularis longus, fibularis brevis, fibularis tertius, fibularis digiti minimi, and even the so-called 'extensor digitorum lateralis': see, e.g., Lewis, 1989; Russell, 1993; Hutchinson, 2002; Russell & Bauer, 2008; see also Table 2).

³The considerations made for modern humans apply to rats, with the difference that rats do not have a brachioradialis nor an extensor pollicis brevis, but have an extensor digiti quarti. Concerning the anterior leg muscles, rats have an extensor digitorum longus, extensor hallucis longus and a tibialis anterior, as modern humans, but do not have a fibularis tertius.

⁴Apart from the posterior leg muscles (Table 2), modern humans have six muscles in the leg: the fibularis longus and fibularis brevis, in the lateral compartment, and the tibialis anterior, extensor digitorum longus, fibularis longus and extensor hallucis longus, in the anterior compartment. The fibularis longus, fibularis brevis and fibularis tertius are discussed in Table 2. The extensor digitorum longus and extensor hallucis longus 'correspond' topologically to the extensor digitorum and to the extensor pollicis longus of the forearm, respectively (e.g. Quain *et al.*, 1894). As explained in the text, the extensor antebrachii et carpi radialis of lizards has a clear 'correspondence' to the tibialis anterior, but rats and modern humans have two 'extensor carpi radialis' muscles, i.e. the extensor carpi radialis longus and the extensor carpi radialis brevis, so in these taxa the tibialis anterior has no clear, direct muscle-to-muscle 'correspondence' with a single individual muscle of the forearm (see also the comments about the ontogeny of these muscles in Table 2). Regarding the muscles that lie on the dorsum of the foot, these are the extensor digitorum brevis, which usually goes to the extensor expansions of digits 2, 3 and 4, and the extensor hallucis brevis, which goes to the extensor expansion of digit 1. The extensor indicis of the hand clearly 'corresponds' to the part of the extensor digitorum brevis of the foot going to digit 2, so it does not 'correspond' to a single, separate muscle in the foot (e.g. Quain *et al.*, 1894). As is explained in more detail in the text, the evident topological 'correspondence' between the extensor hallucis brevis and the extensor pollicis brevis and between the extensor pollicis longus and the extensor hallucis longus is an example of how these 'correspondences' are not the product of a true homology, or 'ancestral body plan', but instead of homoplasy, i.e. of independent evolution. This is because the extensor hallucis brevis is a short extensor of the foot (derived from the extensores digitorum breves) while the extensor pollicis brevis is a very recent structure derived from the abductor pollicis longus, which is not part of the short extensors of the hand (the short extensor of the hand going to digit 1 is actually the extensor pollicis longus: see, e.g., Lewis, 1989; Diogo & Wood, 2011, 2012).

DeLaurier *et al.* (2006), in which *Pitx1* and *Tbx4* were ectopically misexpressed in the mouse forelimb using transgenic methods. Skeletal preparations of newborn *Pitx1* transgenic embryos show a partial transformation of forelimb skeletal elements to reflect characteristics of the wild-type hindlimb knee. For instance, in hemizygote transgenics the

distal humerus is broadened at the elbow to resemble the shape of a femur, and the head of the radius is increased in size and is similar to the head of the tibia, the olecranon process of the ulna being reduced in size. In the *Prx1-Pitx1* homozygote transgenics, transformation of the elbow region is more extreme, the distal head of the humerus

Table 4. Scheme illustrating hypotheses regarding the homologies of the hand muscles of adults of representative tetrapod taxa (adapted from Diogo & Abdala, 2010; see legend to Table 1 for further details)

<i>Ambystoma mexicanum</i> [five hand muscles/muscle groups: 5 (100%) seem to 'correspond' directly to foot muscles/muscle groups ¹]	<i>Timon lepidus</i> [seven hand muscles/muscle groups: 5 (71%) seem to 'correspond' directly to foot muscles/muscle groups ²]	<i>Rattus norvegicus</i> [11 hand muscles/muscle groups: 7 (64%) seem to 'correspond' directly to foot muscles/muscle groups ³]	<i>Homo sapiens</i> [13 hand muscles/muscle groups: 10 (77%) seem to 'correspond' directly to foot muscles/muscle groups ⁴]
—	—	Palmaris brevis (derived from flexores breves superficiales)	Palmaris brevis (derived from flexores breves superficiales)
—	Lumbricales [Lumbricales]	Lumbricales [Lumbricales]	Lumbricales [Lumbricales]
Contraahentes digitorum [Contraahentes digitorum]	Contraahentes digitorum [Contraahentes digitorum]	Contraahentes digitorum [Contraahentes digitorum]	—
—	—	Adductor pollicis	Adductor pollicis [Adductor hallucis: ≠ ontogeny]
—	—	—	'Volaris primus of Henle' [Interosseus plantaris hallucis ']
Interphalangeus digiti 3 [Interphalangeus digiti 3]	—	—	—
Flexores breves profundi [Flexores breves profundi]	Flexores breves profundi [Flexores breves profundi]	Flexores breves profundi [Flexores breves profundi]	Flexor brevis profundus 2 ('deep head of flexor pollicis brevis') [Flexor brevis profundus 2] (lateral head of flexor hallucis brevis)
—	—	—	Interossei palmares 1–3 (flexores breves profundi 4,7,9) [Interossei plantares]
—	—	—	Interossei dorsales 1–4 (flexores breves profundi 3,5,6,8 + int. 1,2,3,4) [Interossei dorsales]
—	—	Flexor pollicis brevis [Flexor hallucis brevis]	Flexor pollicis brevis ('superficial head of flexor pollicis brevis') [Flexor hallucis brevis] (medial head of flexor hallucis brevis)
—	—	—	Opponens pollicis
—	—	Flexor digiti minimi brevis [Flexor digiti minimi]	Flexor digiti minimi brevis [Flexor digiti minimi]
—	—	Opponens digiti minimi	Opponens digiti minimi
—	Abductor pollicis brevis	Abductor pollicis brevis	Abductor pollicis brevis [Abductor hallucis]
Abductor digiti minimi ('extensor lateralis digiti IV') [Abductor digiti V]	Abductor digiti minimi [Abductor digiti minimi]	Abductor digiti minimi [Abductor digiti minimi]	Abductor digiti minimi [Abductor digiti minimi]
Intermetacarpales [Intermetatarsales]	Intermetacarpales [Intermetatarsales]	Intermetacarpales [Intermetatarsales]	—
—	Dorsometacarpales	—	—

int, intermetacarpales.

¹As stressed by Walthall & Ashley-Ross (2006) the hand and the foot muscles of salamanders (e.g. *Taricha torosa*) are strikingly similar, all the muscles/muscle groups of the hand having a clear 'equivalent' in the foot; this is particularly remarkable because these salamanders have five digits in the foot and only four digits in the hand. It should be noted that our recent studies of *Ambystoma mexicanum* confirmed that they have a muscle interphalangeus digiti 3 in the hand connecting the metacarpophalangeal and first interphalangeal joints of digit 3, as reported by, e.g. Grim & Carlson (1974). This muscle clearly 'corresponds' to the muscle interphalangeus digiti 3 of the foot, which connects the metatarsophalangeal and first interphalangeal joints of digit 3 (our recent studies also revealed that in this species, contrary to the hand, digit 4 of the foot has a similar muscle interphalangeus as well as a more distal muscle seemingly connecting the first and second interphalangeal joints).

²All the hand muscles/muscle groups of lizards have a clear, direct 'equivalent' in the foot, with the exceptions of the dorsometacarpales and the abductor pollicis (there is usually no intrinsic abductor hallucis—brevis—muscle in the foot: see, e.g., Lewis, 1989; Russell, 1993; Russell & Bauer, 2008).

³The considerations made for modern humans apply to rats, with the difference that rats do not have a 'volaris primus of Henle' nor an opponens pollicis in the hand, that the intermetacarpales/intermetatarsales are not fused to the flexores breves profundi 3, 5, 6 and 8 to form the dorsal interossei in the hand and foot, and that these mammals have a series of contraahentes digitorum in the hand and foot [i.e. adductor muscles running mainly from the contraahens fascia to digits other than digit 1; it should be noted that Greene (1935) stated that rats have dorsal and palmar/plantar interossei, but the descriptions actually point out that these mammals have a full series of flexores breves profundi in both the hand and foot, and this was confirmed by our dissections and a review of the literature: see, e.g. Diogo & Abdala (2010)]. In rats the adductor hallucis and the abductor hallucis are usually not present as distinct, separate muscles [e.g. the abductor hallucis seems to be completely missing or fused with the flexor hallucis brevis: see, e.g. Greene (1935)].

⁴In general, in modern humans the muscles of the hand are strikingly similar to those of the plantar surface of the foot, not only functionally and topologically but also concerning their pattern of innervation; the foot muscles 'corresponding' to the hand muscles innervated by the median nerve are innervated by the median lateral plantar nerve, while those 'corresponding' to the hand muscles innervated by the ulnar nerve are innervated by the lateral plantar nerve, with almost no exceptions (and these very few exceptions can be logically identified if one takes into account that in the hand the functional axis is digit 3 while in the foot it is digit 2, e.g. in both the hand and foot the lumbricales that are associated with the digits that lie between the functional axis and digit 5—i.e. lumbricales 3 and 4 in the hand and lumbricales 2, 3 and 4 in the foot—are all innervated by the ulnar/lateral plantar nerves). It should however be noted that, as it will be explained in more detail in the text, both the transverse and oblique heads of the adductor pollicis are mainly derived ontogenetically from the anlage of contraahens 1, while in the foot the oblique head of the adductor hallucis is derived from the anlage of contraahens 1 but the transverse head is derived from a different, neomorphic anlage of the contraahens layer (e.g. Cihak, 1972). A peculiar muscle of the plantar surface of the foot

is the quadratus plantae, and a peculiar muscle of the hand is the palmaris brevis (one could argue that these muscles could ‘correspond’ to each other, e.g. based on the fact that they are innervated by the lateral plantar nerve and the ulnar nerve, respectively, but they are topologically very different from each other, because the former runs from the calcaneus to the tendons of the flexor digitorum longus, while the latter is a superficial muscle running from the palmar aponeurosis to the skin of the hypothenar region of the hand; moreover, the palmaris brevis seems to derive from the anlage of the flexores breves superficiales while the quadratus plantae seems to derive from the anlage of the flexor hallucis longus: e.g. Cihak, 1972; Diogo & Wood, 2012). The opponens pollicis and the opponens digiti minimi do not have clear ‘equivalents’ in modern humans, but they do have ‘equivalents’ in various primates (opponens hallucis and opponens digiti minimi: e.g., Lewis, 1989). The ‘volaris primus of Henle’ is often considered to be a ‘first palmar interosseous’, going to the thumb, but as explained by Diogo & Wood (2011, 2012), the true first palmar interosseous going to the thumb is very likely the flexor brevis profundus 2, which very likely corresponds to the so-called ‘deep head of the flexor pollicis brevis’ of human anatomy but is in fact a separate muscle derived from a separate primordium (Cihak, 1972) and with a distinct innervation (it is usually innervated by the deep branch of the ulnar nerve, while the ‘superficial head of the flexor pollicis brevis’ is usually innervated by the median nerve). In the foot, the ‘volaris primus of Henle’ is mirrored by the ‘interosseous plantaris hallucis’ (*sensu* Cihak, 1972), while the ‘deep head of the flexor pollicis brevis’ is mirrored by the ‘lateral head of the flexor hallucis brevis’, which is also in reality a separate muscle derived from a separate primordium (Cihak, 1972) and with a distinct innervation (it is usually innervated by the lateral plantar nerve and/or by an anastomosis between this nerve and the medial plantar nerve, while the ‘medial head of the flexor hallucis brevis’ is usually mainly innervated by the medial plantar nerve).

is more similar to the distal femur and the shape of the proximal head of the single zeugopodal element resembles the shape of the proximal tibia, and there is thus no element resembling the ulna. Regarding the wrist, in transgenic mice the scapholunate bone resembles the talus in the ankle, while the pisiform and triquetral are apparently fused to form a structure similar in shape to the calcaneus of the ankle. These changes are accompanied by changes in the muscles as well. In both hemizygote and homozygote transgenic mice the extensor carpi radialis has a single distal tendon, which inserts onto digit 2 in hemizygotes and onto digit 1 in homozygotes, thus resembling the tibialis anterior, particularly in the hemizygote condition with an insertion to digit 1 (see Table 3). Also, in the transgenic mice the extensor indicis proprius is not present in its normal location in the forearm and is instead translocated distally to the wrist region to originate from the calcaneus-like bone present in the wrist, thus having a topology that is strikingly similar to that of the extensor digitorum brevis of the hindlimb, which usually originates from the calcaneus (see Table 3). These changes seem to be due to the fact that misexpression of *Pitx1* induces ectopic expression of hindlimb-restricted markers (e.g., *Hoxc10*) in the forelimbs of hemizygous and homozygous transgenic mice; however, expression of forelimb-restricted markers is unaffected, which may explain why some structures of the transgenic limb retain some forelimb traits.

Our results provide a new, puzzling insight to the specific issues discussed above and to the forelimb/hindlimb enigma in general. Of the forelimb muscles shown in Tables 1–4, the arm (stylopod) muscles are clearly those ones that are less similar to hindlimb muscles (0% of clear, muscle to muscle topological ‘correspondence’ in salamanders, lizards, mice and modern humans). In lizards, and particularly in salamanders, the ventral and dorsal forearm (zeugopod) and hand (autopod) muscles are striking similar to the posterior leg, anterior leg and foot muscles, respectively (78, 100, and 100% of ‘correspondence’ in salamanders, respectively). The ventral forearm and particularly the hand musculature of derived tetrapods such as modern humans exhibit numerous similarities with the posterior leg and foot (75 and 77% of ‘correspondence’, respectively).

However, interestingly, the dorsal forearm muscles have become more different from the anterior leg muscles, e.g. only 3 of the 12 dorsal forearm muscles of modern humans (i.e., 25%) have a direct ‘equivalent’ in the leg. In total, of the 22 arm, forearm and hand muscles/muscle groups of salamanders, 18 (78%) have direct ‘equivalents’ in the hindlimb; the numbers for lizards are 14/24 (58%), for mice 14/35 (40%), and for modern humans 19/37 (51%). Therefore, if we only take into consideration the total percentages, these data seem to provide some support for the hypothesis of plesiomorphic similarity and subsequent evolutionary divergence, because there is e.g. 78% *vs.* 51% of ‘correspondence’ in phylogenetically plesiomorphic tetrapods such as salamanders *vs.* phylogenetically derived tetrapods such as modern humans.

However, if we analyze the data in more detail and take into account the total number of individual forelimb elements with clear ‘correspondences’ in the hindlimb, we come to a conclusion that, to our knowledge, has never been put forward, at least not based on comparative empirical data: in modern humans the total number of forelimb muscles with a clear hindlimb ‘equivalent’ ($N = 19$) is substantially higher than in other mammals such as rats ($N = 14$), reptiles such as lizards ($N = 14$) and, remarkably, even in phylogenetically (and, as is usually argued in the literature, anatomically: e.g., Owen, 1866; Humphry, 1872*a, b*; Howell, 1935) plesiomorphic tetrapods such as salamanders ($N = 18$). Even if one only takes into account the percentage of direct similarity, it is notable that in both the ventral forearm and hand lizards (63; 71%) and rats (63; 64%) have a lower percentage than salamanders (78; 100%), but then modern humans exhibit a percentage (75; 77%) that is higher to that found in the two former taxa and almost similar, in the case of the ventral forearm, to that found in salamanders. This corroborates the idea that evolutionary divergence and evolutionary convergence/parallelism have both played a crucial role, and been somewhat counterbalanced, in the evolution of the tetrapod fore and hindlimbs.

That is, there is evolutionary divergence, leading to some differences between the forelimb and hindlimb musculature that are not seen in plesiomorphic tetrapods such as salamanders, but there is also a substantial evolutionary

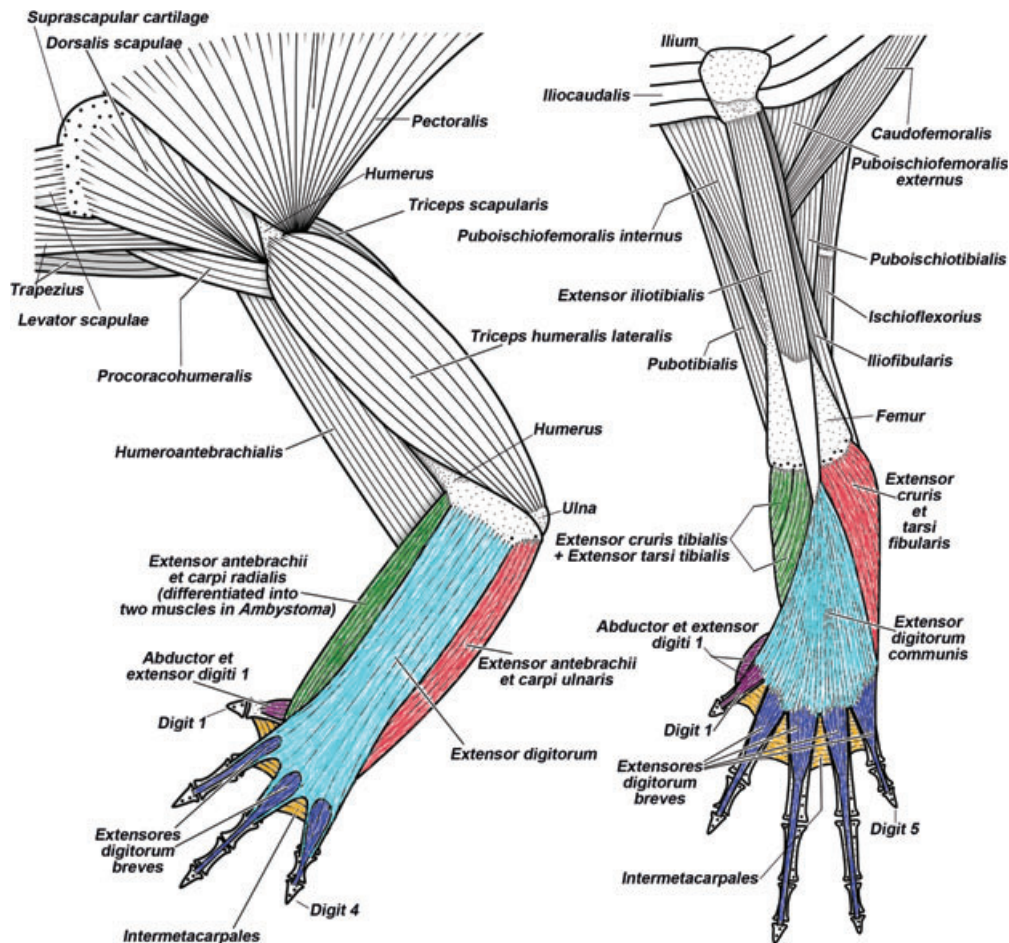


Fig. 2. Superficial musculature of the forelimb (on the left) and the hindlimb (on the right) in dorsal view, showing the striking similarities between the muscles of the forearm and autopodium and the differences between the muscles of the arm and girdles in the urodele *Taricha torosa*, which differs little from *Ambystoma mexicanum* in its limb muscles [modified from Walthall & Ashley-Ross (2006); N.B., as this is a dorsal view and Fig. 1 is a palmar/plantar—i.e., ventral—view, there is no correspondence between the colours used in the two figures, i.e. they do not represent homologous structures between urodeles and modern humans].

parallelism/convergence; e.g. cases of phylogenetically independent evolution have occurred even within highly derived tetrapod clades such as primates, leading to strikingly similar structures such as those seen in modern humans. For instance, the adductor hallucis and adductor pollicis of humans are particularly similar to each other because both these muscles have well-differentiated transverse and oblique heads. However, contrary to the two heads of the adductor hallucis, which are well differentiated in phylogenetically plesiomorphic primates such as lemurs, within primates the two heads of the adductor pollicis only became well differentiated in the node leading to catarrhines (old world monkeys + hominoids; Diogo & Wood, 2011). This provides an illustrative example of structures of the hand and foot that clearly mirror each other but that have not only very different evolutionary, but also ontogenetic, origins: as shown in the developmental study of Cihak (1972), the transverse head of the adductor pollicis derives from the anlage of the contrahens 1, while the transverse head of the adductor hallucis derives from a neomorphic anlage of the contrahens fascia that is not

part of the anlage of the contrahens 1. As also explained above, in both the hand and foot of modern humans there are three palmar/plantar interossei, which adduct the digits, and four dorsal interossei, which abduct the digits. However, this is again clearly the result of independent evolution, because the plesiomorphic condition for primates, seen in, e.g., lemurs, is not to have dorsal and palmar interossei in the hand, but instead ten flexores breves profundi and four intermetacarpales that are not fused to form (as they usually form in hominoids) the interossei (Diogo & Wood, 2011). Another example concerns the presence of a flexor pollicis longus and of a flexor hallucis longus in modern humans. These muscles are very similar to each other, inserting onto the distal phalanx of the thumb and of the big toe, respectively, but only the latter muscle is often present in mammals and in most primates: the flexor pollicis longus is plesiomorphically missing in primates and was only acquired, independently, in hylobatids and in humans (Diogo & Wood, 2011).

Another example concerns the so-called ‘volaris primus of Henle’ (a short, thin muscle that usually goes to the ulnar side

of the base of the proximal phalanx of the thumb), which is only consistently present (i.e. in > 50% of cases) in modern humans within primates, and which mirrors the ‘interosseous plantaris hallucis’ (*sensu* e.g. Cihak, 1972, i.e. a short, thin muscle that usually goes to the lateral side of the base of the proximal phalanx of the thumb). A further example concerns the extensor hallucis brevis, which derives from the medial portion of the anlage of the extensor digitorum brevis, i.e. it is clearly a short extensor of the foot (e.g. Lewis, 1910, 1989; Cihak, 1972). By contrast, in the hand the ‘corresponding’ muscle, extensor pollicis brevis, is a very recent structure (independently acquired in hylobatids and humans only, within primates) that derived from a muscle that is not part of the short extensors of the hand, i.e. the abductor pollicis longus (see, e.g. Lewis, 1989; Diogo & Wood, 2011, 2012). One last example concerns the palmaris longus/plantaris: the plantaris seemingly derives from the anlage that gives rise to the gastrocnemius, which is somewhat similar to the forelimb anlage of the flexor antibrachii et carpi ulnaris; the palmaris longus seemingly derives both from the anlage that gives rise to the flexor digitorum profundus plus the proximal part of the flexor digitorum superficialis in the forearm and from the anlage of the flexores breves superficiales in the hand (e.g. Lewis, 1910, 1989; Diogo & Wood, 2011, 2012; Tables 1–4). Consequently, the ontogeny of the flexor digitorum superficialis/flexor digitorum brevis is also different, because the latter derives from the anlage of the flexores digitorum breves of the foot while the former derives from both the anlage of the flexores breves superficiales of the hand and the forearm anlage that gives rise to the flexor digitorum profundus (Lewis, 1989; Diogo & Wood, 2011, 2012; Tables 1–4).

These remarkable cases of independent, homoplastic evolution within the primate clade seem at first particularly difficult to explain, but they actually reinforce the idea of evolutionary parallelisms (see Diogo, 2005), although as it will be seen below this is not the whole story. As stressed by Young & Hallgrímsson (2005), hindlimbs and forelimbs will tend to covary (i.e. evolve in a similar way) because they share similar developmental factors, i.e. evolutionary changes would tend to affect both limbs in a parallel manner. Their morphometric study revealed that in primates there is effectively a significant covariation between the hard tissues of the hand and foot; this might help to explain some of the remarkable cases of homoplastic evolution of the hand and foot muscles within this clade. It is important to note that modern humans are not particularly special within primates or even within non-primate tetrapods, just because they are the species exhibiting a higher number of forelimb muscle elements with clear hindlimb ‘equivalents’ in Tables 1–4. For instance, our closest living relatives, chimpanzees and gorillas, as well as numerous other primates, often have an opponens digiti minimi, and sometimes also an opponens hallucis, in the foot (e.g. Diogo *et al.*, 2010). So, these primates often have two further hand muscles with clear foot ‘equivalents’ that are not found in the hand of modern humans (Table 4).

IV. GIRDLE MUSCLES, LIMB NERVES, PHYLOGENETIC CONSTRAINTS, AND THE COMPLEX PATTERNING OF LIMB MUSCULATURE

Regarding the configuration of the girdles and stylopods of the pelvic and pectoral appendages in modern humans, it is clear that there are crucial differences regarding both the general disposition and the specific configuration of each nerve (e.g. Quain *et al.*, 1894; Netter, 2006). The brachial plexus and the sacral/lumbar plexus are very different from each other, and the flexor muscles in the thigh (semitendinosus, semimembranosus, and biceps femoris) are innervated by the tibial nerve, which then extends distally to innervate all the muscles of the leg and foot, while the flexor muscles in the arm (biceps brachii, brachioradialis and brachialis) are mainly innervated by the musculocutaneous nerve, which does not innervate any muscle in the forearm and hand. However, despite the fact that the tibial nerve runs between and innervates the extensors in the leg and that the medial and ulnar nerves run between and innervate the flexors in the forearm, in the plantar region of the foot the lateral and medial branches of the tibial nerve clearly ‘behave’ respectively as the ulnar and median nerves of the palmar region of the hand (see Section I). This reinforces the idea that the proximal regions of the fore and hindlimb are more different from each other because they come from the modification of structures that were already fully formed, and were substantially different early in the transitions from fins to limbs. This would represent a case of a phylogenetic constraint where the pelvic girdle and its muscles are very different from the pectoral girdle and its muscles already in sarcopterygian fish (e.g. see figs 2.3 and 2.4 in Coates & Ruta, 2007; see also Diogo, 2007). By contrast, the distal regions of the hindlimbs and of the forelimbs are more similar to each other because they include neomorphic structures, i.e. the ontogenetic/functional/topological constraints were almost totally prevalent (relatively to the phylogenetic constraints) and thus led to the formation of strikingly similar muscles that have very similar (but clearly homoplastic) patterns of innervation.

This becomes evident also from a comparison of the distal muscles of the fore and hindlimb. For instance, in modern humans the hand and foot muscles are strikingly similar (see above and Table 4), but the pelvic/gluteal and pectoral muscles are remarkably different. Of course, in the past authors have looked intensively to any type of possible ‘homology’ between these latter muscles, and have even elaborated strict hypotheses of ‘muscular homologies’ for each of these muscles (e.g. Quain *et al.*, 1894). But in general these hypotheses do not stand up to detailed scrutiny (e.g. Diogo & Abdala, 2010). For example, according to such homology hypotheses, the trapezius, sternocleidomastoideus, rhomboideus major, rhomboideus minor, levator scapulae and serratus anterior are ‘homologous’ to the external oblique and to the lumbar aponeurosis. However, the former six muscles have

very different evolutionary and developmental origins: the trapezius and sternocleidomastoideus do seem to derive from somites but also receive a partial contribution from the head muscle anlagen and/or nerves, while the serratus anterior, levator scapulae, rhomboideus major and rhomboideus minor derive from axial (body) muscle anlagen that become connected to the pectoral girdle (e.g. Edgeworth, 1935; Diogo & Abdala, 2010). Also, according to such homology hypotheses the coracobrachialis is ‘homologous’ to the obturator internus, obturator externus, quadratus femoris and/or adductor magnus (i.e. with gluteal and medial muscles of the thigh), while the biceps brachii and brachialis are ‘homologous’ to the semimembranosus, semitendinosus and biceps femoris (i.e. with posterior muscles of the thigh). However, in the forelimb the coracobrachialis, biceps brachii and brachialis are all flexors of the arm, and share a similar evolutionary and ontogenetic origin, and are all innervated by the same nerve, the musculocutaneous (Table 1). Our dissections and comparisons, as well as the studies of other researchers, indicate that other tetrapods, including phylogenetically plesiomorphic taxa such as salamanders, also exhibit this pattern of striking similarities between the forearm/hand and the leg/foot muscles *versus* substantial differences between the pectoral and pelvic girdle (see, e.g. Walthall & Ashley-Ross, 2006). The remarkable similarity between the forearm and hand and leg and foot muscles found in salamanders such as *Taricha torosa* and *Ambystoma mexicanum* (Table 4) is particularly remarkable not only because these muscles had a phylogenetically independent evolution (see below, Section V), but also because these salamanders have five digits in the foot and only four digits in the hand. For instance, in these salamanders the most ulnar digit of the hand, digit 4, has a separate muscle abductor digiti minimi that clearly mirrors the abductor digiti minimi of the most lateral digit of the foot, digit 5, as well as digit 5 of the hand of most other tetrapods (Table 4). Furthermore, the fleshy parts of the extensores digitorum breves of digits 1 and 4 of the hand are much shorter than those of the other hand digits, while in the foot the shorter fleshy parts of these muscles are those of digits 1 and 5. This suggests that the overall configuration of the muscles is mainly related to the position, rather than the ‘identity’ of the digits (as defined by comparative anatomists and paleontologists *versus* by evolutionary developmental biologists); i.e. the muscles of the hand behave as if digit 4 is in reality digit 5 because, due to the absence of digit 5, digit 4 is now the most ulnar digit in the hand [for a recent review of the different definitions of ‘identity’ and about this issue in general, see Diogo & Abdala (2010)]. A further example that the muscles of the hand of *A. mexicanum* behave as if digit 4 corresponds to digit 5, and not digit 4, of the foot is that in the foot digits 3 and 4 have one or more interphalangeal muscles, while in the hand only digit 3 has an interphalangeal muscle.

Developmental studies carried out in recent years have revealed that there are also important differences in the expression patterns associated with the morphogenesis of the proximal regions of the forelimb and of the hindlimb

that are not seen in the most distal regions of these limbs (e.g. *Hox9* paralogs are active in the arm but not in the thigh: see, e.g., fig. 1 of Young & Hallgrímsson, 2005). Studies have also shown that the formation of the muscles of the proximal forelimb occurs through mechanisms that are markedly different from those leading to the formation of the muscles of the distal forelimb (i.e. of the arm, forearm and hand muscles, which arise through the classic and well-studied migration from the somites to the limb bud): (i) the superficial girdle muscles (‘appendicular pectoral girdle muscles’ *sensu* Diogo & Abdala, 2010; e.g. pectoralis major and latissimus dorsi) develop by an ‘In-Out’ mechanism whereby migration of myogenic cells from the somites into the limb bud is followed by their extension from the proximal limb bud out onto the thorax; (ii) the deep girdle muscles (‘axial pectoral girdle muscles’ *sensu* Diogo & Abdala, 2010; e.g. rhomboideus, serratus anterior) are induced by the forelimb field which promotes myotomal extension directly from the somites (Valasek *et al.*, 2011). According to Valasek *et al.* (2011) the appearance of the forelimb is followed by pectoral girdle development which braces the distal limb to the axial skeleton; the limb program was able to induce and recruit axial structures for its anchorage—the medial scapular border in mammals and the scapular blade in birds (as well as the deep girdle muscles and possibly even the cleithrum and sternum, according to them). The ‘In-Out’ mechanism has already proven useful to help understand why in the evolution of the peculiar body shape of turtles the superficial girdle muscles changed their proximal origin (e.g. latissimus dorsi originates from nuchal bone and not from lumbar region) while the deep girdle muscles changed their distal insertion (e.g. rhomboid-levator scapulae complex attaches to scapula but also to plastron regions derived from clavicle and interclavicle; Nagashima *et al.*, 2009). Another important difference between the proximal limb and the distal limb is that in the proximal limb tendons are induced but do not segregate to form specific tendons in the absence of muscles, while in the distal limb (e.g. autopod), where muscles are only present at later ontogenetic stages, tendon formation is initiated and segregation into individual tendons occurs in the absence of muscles (these distal tendons will however later require muscle contact, and will degenerate in a muscle-less limb environment; Hasson, 2011).

Kardon (1998) provides one of the most complete studies on the ontogeny of the tendons and muscles of the hindlimb of chickens, and shows that, regarding the muscles: (i) muscle patterning begins with the migration and aggregation of myoblasts into the dorsal and ventral region of the limb, which are thus the first two muscle masses to differentiate; (ii) then each of these two masses become further divided into three masses lying in between the three pairs of tendon primordia (located dorsally and ventrally superficial to the knee, to the intertarsal part of the ankle and to both the metatarsal/phalangeal and interphalangeal joints, respectively), resulting in the formation of thigh, leg and foot muscles; (iii) from their initial appearance within the thigh, leg and foot muscle masses, most myotubes are arranged in

a highly structured array and their fibre orientation correctly predicts the fibre orientation of the future individuated muscles of which the myotubes will be a part; (iv) the final event is the physical segregation of muscle masses, which apparently does not follow an overall organization to their sequence, with three main exceptions: (i) the muscles generally differentiate from proximal to distal, (ii) the dorsal muscles in general differentiate before the ventral, and (iii) in the ventral mass the long flexors of the digits form before the short flexors of the digits so their tendons can go straight to the distal phalanges of the digits and so the tendons of the short flexors then bifurcate and go to the middle phalanges of the digits. A general conclusion of Kardon's (1998) study is that the timing and mechanism of tendon attachment to cartilage differs between different regions of the limb. Tendons derived from the proximal tendon primordium attach to their cartilage origin and insertion sites nearly concurrently with their formation, as a consequence of the early connection between the proximal tendon primordium and underlying cartilages. However, tendons derived from the intermediate and distal tendon primordia lie initially subjacent to the ectoderm and only later attach to the appropriate cartilage sites, many of which form much later in development. According to Kardon (1998), these and other differences between the proximal and intermediate tendons and the distal tendon thus seem to confirm that the morphogenetic processes governing tendon development are quite different in the foot from the rest of the hindlimb, thus supporting the idea that the tetrapod digits are *de novo* (i.e. neomorphic), and not ancient structures (i.e. formed by skeletal elements that correspond directly to elements that were/are present in non-tetrapod vertebrates).

Kardon's (1998) work is very important for the subjects discussed herein, because it helps to explain some of the superficial (e.g. the divisions in dorsal and ventral muscle masses and the subdivision of each of these masses into three masses separated by the three tendon primordia) as well as a few of the more specific (e.g. the long flexors forming first to attach onto the distal phalanges so that the short flexors then bifurcate and attach to more proximal phalanges) similarities between the hindlimb and forelimb muscles due to similar developmental constraints/pathways. In addition, the suggestion that the foot and hand are neomorphic features might also explain the particularly striking similarities of the foot and hand muscles of tetrapods, as explained above. However, an important point is that, as stressed by Kardon (1998), there is seemingly no overall, strict organization plan to explain the specific sequence in which all, or even most, individual muscles are formed, such as that proposed by N.H. Shubin and colleagues to explain the formation of the individual skeletal elements of the limbs (e.g. Shubin & Alberch, 1986). There is rather a highly complex pattern of muscle splitting, as elegantly shown in fig. 5 in Kardon (1998). This complexity was also emphasized in one of the few comprehensive studies on the spatial and temporal patterns of muscle cleavage in the chick thigh, which revealed

much more complex separation patterns between muscles than previously described (Schroeter & Tosney, 1991, pp. 325, 344; see also Hasson, 2011, p. 1102). It is therefore particularly hard to understand how phylogenetically independent evolution led to the striking and highly complex similarity seen in the forearm/hand and leg/foot muscles of both phylogenetically plesiomorphic and derived tetrapods, particularly if one takes into account the very complex, highly dynamic and apparently mainly epigenetic process of limb muscle-nerve connection reported by authors such as Pettigrew *et al.* (1979).

V. COMPARATIVE ANATOMY, HOMOPLASIES AND CONSTRAINTS: GENERAL REMARKS AND FUTURE DIRECTIONS

In our opinion the lack of a clear explanation about how each individual limb muscle is formed and why there is such striking similarity between the hindlimb and forelimb muscles of the zeugopod and autopod, and thus the persistence of this old, fundamental problem in comparative anatomy, is in large part due to theoretical and historical reasons, and not to the lack of the necessary methods/techniques to address this problem. First, it is largely due to the fact that classic comparative anatomists tried to reduce the incredible complexity of the body to a simple, ideally segmented 'model', or 'archetype', from which all structures of all body parts were derived (see Section I). Then, particularly in the second half of the 20th Century, comparative anatomists began to be rather an exception within the scientific community, and those few remaining tended to focus on more restricted taxa. For instance, the last comprehensive study of the comparative anatomy and development of the head muscles of all major vertebrate groups was published by Edgeworth (1935) more than 75 years ago. During the last decades evolutionary developmental biologists have attempted to revive the practice of comparing and understanding the anatomy of a wide range of animal groups. One example concerns the studies of S. Kuratani and colleagues on the development of both the skeleton and muscles of some vertebrate groups, which have shown, for example, that the evolution of the turtle body plan was associated with both the folding of ancestral and the creation of new muscle connections in the pectoral musculature (Nagashima *et al.*, 2009). Another example concerns the series of excellent recent studies carried out by N. H. Shubin and colleagues, e.g. comparing the development of the pectoral appendages and of the branchial arches of chondrichthyans and osteichthyans and providing evidence to support Gegenbaur's hypothesis that paired appendages arose from modified gill arches (e.g. Gillis, Dahn & Shubin, 2009).

However, some of the encyclopedic and multidisciplinary knowledge accumulated until the second half of the 20th Century precisely by authors such as Gegenbaur, Romer, Owen, Haeckel, DeBeer, Balfour, Goodrich, Kevesten,

Edgeworth, Gadow and others, particularly concerning the broader comparative anatomy of soft tissues, seems to have been somewhat forgotten, or at least to be difficult to compile/use. Very few current researchers know in detail both the hard and soft tissues of groups as diverse as chondrichthyan, actinopterygian and sarcopterygian fish and amphibian, reptilian and mammalian tetrapods. This complicates comparisons among these groups and consequently discussions about the transformations and evolutionary changes that occurred since the appearance of the first paired appendages to the formation of the limbs of extant tetrapods. One notable exception to the scarcity of broad and multidisciplinary comparative anatomical works published in the last decades concerns the studies of Lewis. In his elegant book on the evolution and comparative anatomy of both the skeletal and muscle structures of the hand and foot (Lewis, 1989, pp. 27–28), he wrote that ‘attempts to rationalize the complex morphology of the upper and lower limbs . . . have long provided a speculative diversion; there is little doubt, however, that these arrangements, far from being indicators of an all-pervading system of mirror-image homologies in the limbs, represent specializations, proper to the divergent functional needs of the proximal parts of the individual limb and are projected onto a common basic plan in which preaxial borders and postaxial borders are comparable: tibia equates with radius and great toe with thumb’. Lewis’ (1989) ideas were recently supported by Coates & Ruta (2007, p. 36), who stressed that the skeletal similarities between the tetrapod hind- and forelimbs are the product of independent, and even non-concerted evolution, a statement that unfortunately is not echoed in textbooks and research papers as often as it should be.

The observations, comparisons and discussions provided herein complement the data published by Coates & Ruta (2007) and Lewis (1989). The take-home message is that developmental and evolutionary biologists should acknowledge that it is likely that there is a true serial homology at the molecular level between the paired appendages of early vertebrates as a whole, but not between any of the individual muscles that form the forelimbs and hindlimbs of extant tetrapods. It is now well known that *Tbx4* and *Tbx5* are paralogous genes that arose by duplication of a single, ancestral *Tbx4/5* gene (e.g. Duboc & Logan, 2011). The extant cephalochordate amphioxus possesses a single *Tbx3/5* and lacks paired appendages, whereas all vertebrates with paired appendages express *Tbx5* in the pectoral appendages and *Tbx4* in the pelvic appendages. In addition, a recent revised description of the antiarch placoderm *Parayunnanolepis* provided evidence for the presence of pelvic girdles in antiarchs; as antiarchs are placed at the base of the gnathostome radiation in several recent studies, this finding suggests that all jawed vertebrates primitively possessed both pectoral and pelvic appendages (Zhu *et al.*, 2012). Therefore, effectively there are reasons to suggest that the first appearance of these two pairs of appendages is related to a real duplication, i.e. that they are true serial homologues (however, it is important to note

that some authors dispute that there is true morphological homology even at this basic level of hierarchy: see, e.g. Coates & Cohn, 1998). If we accept this idea of homology, then it would be logical to assume that originally these appendages were morphologically similar to each other, although to our knowledge no fish fossils have been found where both the pelvic girdle and fin are exactly, or even almost exactly, similar to the pectoral girdle and fins. It is also not impossible, although this is the subject of much controversy, that the first paired appendages already had some skeletal elements that are still present as individual elements in the forelimbs and hindlimbs of extant tetrapods; in this case, such elements would be true serial homologues (e.g. it is usually accepted that the proximal pectoral metapterygial mesomere of plesiomorphic sarcopterygians is homologous to the tetrapod humerus, but it is extremely difficult to propose any type of homology between this structure and a specific individual bone of the pectoral appendages of non-osteichthyan fish: see, e.g. Diogo, 2007; Wagner & Larsson, 2007).

However, many of the bones, and surely all the individual muscles, that are found in the fore- and hindlimbs of tetrapods were clearly developed after the first appearance of pectoral and pelvic appendages. Sarcopterygian fishes mainly have adductors and abductors of the fins, and none of these muscles is directly homologous to any individual forelimb and hindlimb muscle found in tetrapods (Diogo & Abdala, 2007, 2010). In fact, as can be seen in Table 4, of all the numerous individual muscles found in the human hand, only one is present in plesiomorphic tetrapods such as salamanders (the abductor digiti minimi). Therefore, all the other hand muscles, as well as almost all the foot muscles that are found in modern humans, evolved after the split between amphibians and amniotes. In fact, it should be noted that recent studies suggest that although there are clear similarities in the developmental molecular pathways associated with the formation of appendicular muscles, there are important differences in the way in which the muscles of the pelvic and pectoral appendages are developed, even in fish. For instance, in bony fish (including sarcopterygians) pelvic fin formation is associated with a myotomal extension to deliver fin muscle precursors adjacent to the forming pelvic fin (Cole *et al.*, 2011). Once in position adjacent to the pelvic fin bud, muscle precursors undergo an epithelial mesenchymal transition and are induced to express *Lbx1* and migrate into the fin mesenchyme to form individual pelvic fin muscles. So, the musculature of the pelvic appendage is generated by a morphogenetic process that possesses characteristics of both the primitive (epithelial myotomal extension, e.g. seen in chondrichthyans) and derived (*Lbx1*-positive migratory mesenchymal myoblast precursors, e.g. seen in bony fish and tetrapods) modes of muscle formation in vertebrate pectoral appendages. A recent study with mice also pointed out that there are fundamental differences in the patterning mechanisms governing the establishment of forelimb and hindlimb fields; whereas forelimb antero-posterior (AP) patterning is established by the activity of

paralogous *Hox* genes along the body axis, other non-*Hox* genes and/or more complex combinations of posterior *Hox* genes might have been co-opted for the activity in the hindlimbs (Xu & Wellik, 2011).

Interestingly, morphological similarity in the muscles of fore- and hindlimbs in *Homo sapiens* is not always underlined by a common developmental origin, because 5 of the 19 forelimb muscle elements of modern humans with a clear hindlimb topological ‘equivalent’ derive from embryonic anlagen that are very different from those giving rise to their hindlimb ‘equivalents’ (palmaris longus, flexor digitorum superficialis, extensor pollicis brevis, extensor pollicis longus, adductor hallucis: see above and Tables 1–4). This corroborates our conclusion that the similar muscle structures found in the forelimb and hindlimb of tetrapods such as modern humans are clearly not serial homologues, but instead the result of phylogenetically independent evolutionary changes leading to a parallelism/convergence due to: (i) developmental constraints, i.e. similar molecular/genetic mechanisms are involved (but not as similar as previously thought, as noted above), particularly in the formation of the neomorphic distal region of the limbs, but this does not necessarily mean that similar embryonic anlagen are being used to form the similar adult structures; (ii) functional constraints, related to similar adaptations (e.g. apes have opposable feet and opposable hands, and, accordingly, they frequently have an opponens pollicis/hallucis and an opponens digiti minimi in the hand and foot); (iii) topological constraints, i.e. limited physical possibilities (e.g. an abductor of the big toe needs to attach on the tibial side of that digit as an abductor of the thumb needs to attach on the radial side of that digit); and even (iv) phylogenetic constraints, which tend to prevent/decrease the occurrence of new homoplastic similarities, but help to preserve older, ancestral homoplastic similarities (e.g. modern humans are bipeds but the configuration of their forelimb muscles is in general very similar to those of the apes, which are mainly brachiators and use the forelimb and hindlimb in somewhat similar ways, and even to those of other primates, which are quadrupeds).

Regarding the relationship between muscle similarity and the kind of locomotion in tetrapods (quadrupedal or bipedal) our data contradict the hypothesis that bipedal species would show less similarity than quadrupedal species because the former perform different functions with their fore- and hindlimbs. This is because the total number and also the total percentage of forelimb muscles/muscle groups with a clear hindlimb ‘equivalent’ is higher in modern humans (19/37, i.e. 51%) than in, e.g. quadrupedal mammals such as rats (14/35, i.e. 40%). This provides an illustrative example of how the four types of constraints can be used in different combinations to form the muscles of each specific taxon. In theory, the functional constraints would favour a higher similarity between the forelimb and the hindlimb muscles in quadrupedal taxa than in bipedal groups. However, as noted above the closest living relatives of modern humans, the apes, are mainly brachiators and use the forearms/hands and

legs/feet in a somewhat similar way (e.g. they have opposable hands and feet), so functional constraints played a role in making the forearm/hand muscles strikingly similar to the leg/foot muscles in those species as well. Modern humans no longer have opposable feet, and they no longer have muscles performing in opposition in the foot, but the split between humans and chimpanzees was only about 6 million years (My) ago and, due to phylogenetic constraints, apart from these few differences our forearm/hand and leg/foot muscles remain very similar to those of apes despite the fact that during these 6 My we became obligate bipeds (Diogo & Wood, 2011, 2012). In addition, there are developmental and/or topological constraints that tend to make new structures formed in the forelimb similar to those formed in the hindlimb and *vice versa*, because similar molecular mechanisms are used to form these new structures and/or there are only a few physical/topological possible ways to form, e.g. a flexor or an extensor of one of the only two phalanges of digit 1. So, three of the forearm/hand muscles that are consistently present in modern humans but not in great apes, i.e. that were evolved in the last 6 My of our evolution, mirror leg/foot muscles that were already present in the common ancestor of great apes and humans. The flexor pollicis longus, derived from the anlage of the flexor digitorum profundus, mirrors the flexor hallucis longus that derives from the anlage of the flexor digitorum longus (i.e. the long flexors of the thumb and hallux have similar ontogenies and overall topologies). The ‘volaris primus of Henle’, derived from the anlage of the adductor pollicis and/or flexores breves profundi, mirrors the ‘interosseous plantaris hallucis’, derived from the anlage of the adductor hallucis and/or flexores breves profundi. The extensor pollicis brevis, derived from the anlage of the abductor pollicis longus, mirrors the extensor hallucis brevis that derives from the anlage of the short extensors of the foot (i.e. the short extensors of the thumb and hallux have different ontogenies and proximal attachments, but their distal portions and attachments have a similar topology). In other words, during our evolution towards obligate bipedalism, some similarities between the fore- and hindlimb muscles were lost due to the increased functional divergence between these limbs (e.g. opponens pollicis-opponens hallucis; opponens digiti minimi of the hand-opponens digiti minimi of the foot: see above), while others were gained due to topological and ontogenetic constraints (e.g. flexor pollicis longus-flexor hallucis longus; ‘volaris primus of Henle’—‘interosseous plantaris hallucis’; extensor pollicis brevis-extensor hallucis brevis).

The combination of ontogenetic, topological, functional and phylogenetic constraints thus might also help to solve one of the most crucial questions about the forelimb/hindlimb enigma: why is it that from the first, seemingly serial homologous and thus presumably morphologically similar (see above) pelvic and pectoral appendages was there a significant evolutionary divergence leading to the obvious differences seen in plesiomorphic bony fish and coelacanths, and then a subsequent remarkable evolutionary convergence/parallelism leading to the striking similarity

seen in the fore- and hindlimbs of tetrapods (not only concerning the bones and muscles of the neomorphic foot and hand—autopod—but also of the bones and muscles of the forearm/leg—zeugopod—and of the bones of the arm—stylopod; e.g. compare figs 2.3 and 2.11 in Coates & Ruta, 2007; see also Wagner & Larsson, 2007 and Diogo, 2007)? An example of another important question that needs to be clarified concerns the regulation of limb-type identity and limb-type morphology. As explained above recent studies have shown that misexpression of *Pitx1* in the forelimb leads to a configuration where bones and muscles adopt some characteristics of hindlimbs; when this gene is not expressed in the forelimb region, i.e. in wildtypes, a typical forelimb is formed. Significantly, when *Pitx1* is expressed in the hindlimb region, i.e. in wildtypes, a typical hindlimb is formed, but in *Pitx1*^{-/-} mutant hindlimbs the skeletal elements adopt at least some features that are typical of forelimbs (e.g. the fibula and the tibia have equivalent diameters, the knee joint lacks a patella and the fibula makes contact with the femur, the normal angle between the calcaneus and the footplate is altered, and the ilium fails to form normally contributing to a defective rotation of the hindlimb: e.g. Duboc & Logan, 2011). These data seem to indicate that the ‘default’ configuration for a tetrapod limb (without *Pitx1*) is more similar to the typical configuration of the forelimb than to that of the hindlimb, because when there is no *Pitx1* both limbs adopt typical characteristics of forelimbs. It is crucial to test this hypothesis, and one way in which the data discussed herein could be used to do this would be to study the development, attachments and innervation of each muscle of the *Pitx1*^{-/-} mutant hindlimbs in order to investigate if the muscles simply lose hindlimb morphology without acquiring forelimb characteristics, or if they instead become truly similar to forelimb muscles. It would also be interesting to use the methodology employed herein to test whether our results regarding the relationship between muscle similarity and the locomotion type in tetrapods (quadrupedal or bipedal) are also supported by studies of other tetrapod taxa, particularly birds. We hope that this review will thus be helpful to clarify the evolution of tetrapod limbs, but also to stress that there is still much to be done and re-analyzed about this fascinating subject, thus stimulating future studies that will address these and other questions using a multidisciplinary approach that will focus on both hard and soft tissues.

VI. CONCLUSIONS

(1) There is a true serial homology at the molecular level between the paired appendages of early vertebrates, but not between any of the individual muscles that form the forelimbs and hindlimbs of extant tetrapods.

(2) This is because many of the bones, and surely all the individual muscles, that are found in the fore- and hindlimbs of tetrapods were clearly developed after the first appearance of pectoral and pelvic appendages.

(3) The similar muscle structures found in the forelimb and hindlimb of tetrapods, including modern humans, are therefore the result of phylogenetically independent evolutionary changes leading to a parallelism/convergence due to developmental, functional, topological and phylogenetic constraints.

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