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Cranial or postcranial—Dual origin of the pectoral appendage of vertebrates combining the fin-fold and gill-arch theories?

Rui Diogo

Department of Anatomy, Howard University College of Medicine, Washington, District of Columbia

Correspondence

Rui Diogo, Department of Anatomy, Howard University College of Medicine, 520 W St. NW, Numa Adams Building, Room 1001, Washington, DC 20059, USA.
Email: rui.diogo@howard.edu

Abstract

Two main theories have been used to explain the origin of pectoral and pelvic appendages. The “fin-fold theory” proposes that they evolved from a trunk bilateral fin fold, while Gegenbaur’s theory assumes they derived from the head branchial arches. However, none of these theories has been fully supported. The “fin-fold” theory is mainly often accepted due to some existing developmental data, but recent developmental studies have revived Gegenbaur’s theory by revealing common mechanisms underlying the patterning of branchial arches and paired appendages. Here I review developmental data and many others lines of evidence, which lead to a crucial question: might the apparent contradictions between the two theories be explained by a dual origin of the pectoral appendage, that is, the pectoral girdle and fin/limb being mainly related to the head and trunk, respectively? If this is so then (a) the pectoral and pelvic girdles would not be serial homologues; (b) the term “developmental serial homologues” could only potentially be applied to the pectoral and pelvic fins/limbs. Fascinatingly, in a way this would be similar to what Owen had already suggested, more than 170 years ago: that the pectoral and pelvic girdles are mainly related to the head and trunk, respectively.

KEYWORDS

anatomy, evolution, genetic networks, limbs, molecular mechanisms, muscles, pectoral appendage, pelvic appendage, serial homology, similarity

1 | INTRODUCTION

The origin and evolution of the pectoral and pelvic appendages of vertebrates have been among the most studied and discussed topics within comparative anatomy, developmental biology, evolutionary developmental biology (Evo-Devo), and chordate evolutionary biology. Two major theories have been dominant within these fields regarding the origin of these appendages. The “fin-fold theory,” or “lateral fin-fold” hypothesis of Thacher,¹ Mivart² and Balfour³ claims that these paired appendages

evolved from a bilateral median fin-like structure (Figure 1). This theory was based on the observation of developmental and anatomical similarities among median and paired fins in fishes, assuming that the paired pectoral and pelvic fins evolved from a hypothetical bilateral longitudinal fin fold in a manner similar to that of median fin evolution and development (see recent review of Abe and Ota,⁴ and below). Some decades earlier, comparative anatomist Gegenbaur⁵ proposed a different hypothesis: paired appendages evolved as the result of a transformation of branchial—“gill”—arches,

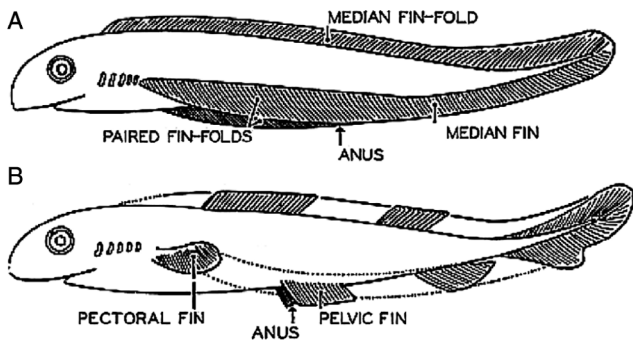


FIGURE 1 Fin-fold theory. A, Ancestral stage, characterized by continuous fin folds, the dorsal and ventral fins posterior to the anus being median and unpaired. B, Paired fin-folds persist only in the region of the pectoral and pelvic appendages, while median fins have become discontinuous (modified from Neal and Rand¹⁰³)

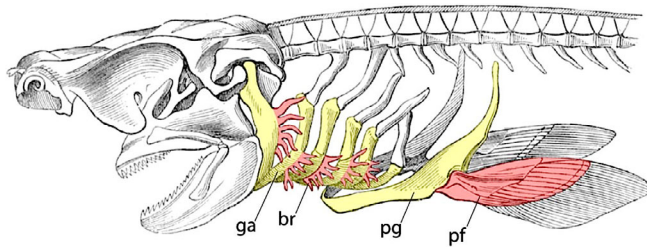


FIGURE 2 Gegenbaur's theory. Shark head skeleton illustrating putative serial homology of the gill arch and pectoral fin skeleton, gill arches (ga) and the pectoral girdle (pg) are in yellow, while branchial rays (br), and the pectoral fin (pf) are in red (modified from Owen⁴⁸ and Gillis and Hall⁶)

with the epi- and ceratobranchial cartilages giving rise to the girdle, and the branchial rays giving rise to the fin proper (Figure 2; see review of Gillis and Hall,⁶ and below).

As noted by Gillis and Hall,⁶ neither of these theories has been truly strongly supported by paleontological data. For instance, according to the fin-fold theory both appendages necessarily appeared evolutionarily at the same time as derivatives of a continuous fin fold, and according to both theories the two appendages should overall be very similar as they would derive from this continuous fold or from similar branchial structures. Instead, the fossil record shows (a) that the pectoral girdle and/or fins seemingly originated earlier in evolution and (b) that in the vast majority of the earlier fishes that did have both of them, these appendages were actually quite different anatomically from each other, particularly their girdle components.⁷⁻³² Therefore, the main reason why most researchers started to be more receptive about the fin-fold theory was because of developmental studies, including, more recently, the discovery of shared expression of

developmental patterning genes between paired and dorsal median fins.^{1,33,34} Another main reason was that Gegenbaur's scheme was deeply influenced by the romantic idea of a polysomeric vertebrate archetype: that is, being formed by many (poly) ancestrally similar "serial homologues" structures (isomeric).³⁵⁻³⁷ This idea has become more and more discredited with time.^{11,38-44} Historically, the idea that the pectoral and pelvic appendages are "serial homologues" was in reality first proposed by Vicq d'Azyr⁴⁵ in 1774, and only later by Oken⁴⁶ and Owen,⁴⁷⁻⁴⁹ two authors that were indeed deeply influenced by Goethe and the German romantics and their obsession by polysomeric "ideal" archetypes.^{11,43,44,50}

This has led to a major, recurrent problem with both the notion of serial homology and the way the links between the pectoral and pelvic appendages are discussed until today: the fact that these topics were originally not framed within an evolutionary context, but instead within an idealized theoretical "archetype" one. That is, although the idea of such an "ideal polysomeric archetype" has been more and more discredited, the a priori assumption that serial homologues, and that the pectoral and pelvic appendages in particular, were necessarily originally similar continues to be highly influential nowadays.^{11-31,43,44} This a priori assumption neglects the fact that in reality the so-called "serial homology" between the pectoral and pelvic appendages postulated by authors such as Oken and Owen actually refers to what is now consensually called "evolutionary parallelism," which is therefore a subset of homoplasy, not of true homology.^{11,43,44} In fact, the most striking examples of similarity between these appendages cited by Owen⁴⁷ mainly refer to highly derived tetrapods such as horses and plesiosaurs, including some in which the pectoral appendages are modified into wings, such as bats. Moreover, Owen specifically used the term "parallelism" to refer to this similarity, much more often than he used "serial homology." For example, when Owen⁴⁸ discussed outgroup lineages to tetrapods, such as chondrichthyans, he clearly stated that those taxa "confused" the notion of "archetype" and "serial homology," because those taxa display a much lower similarity between the pectoral and pelvic appendages. This was in fact explicitly defended by Lankaster, who also stated that the pectoral and pelvic appendages became more similar with time: he considered this and most other cases of so-called "serial homology" to be actually homoplastic events, that is, cases of derived similarity likely due to the influence of forces or similar conditions or "correlations of growth."^{43,44} These historical facts are unfortunately not taken into account by most researchers now working on the evolution and development of these appendages, leading to the current conceptual difference between how developmental

biologists and evolutionary biologists refer to the supposed “serial homology” between the pectoral and pelvic appendages. That is, the former tend to emphasize similar developmental mechanisms (“developmental serial homology” sensu Wagner^{38–42}) while the latter tend to stress both anatomical similarity and evolutionary continuity (“historical serial homology” sensu Wagner³⁸ and Brigandt⁵¹) (see below). It is important to clarify that, from now on, and throughout the discussions provided below, when I refer to serial homology I am using the “historical,” and not the “developmental,” definition of serial homology.

Interestingly, as will be discussed in detail below, recent developmental studies have somehow revived Gegenbaur’s theory, for example, by revealing common mechanisms underlying the patterning of branchial arches and paired appendages.^{6,52} Moreover, as it will also be discussed below, recent comparative studies have shown that the pelvic and pectoral girdles are not only different from each other with respect to the skeleton as seen in most taxa, both extinct and extant: their soft tissues—for example, muscles (Figure 3), arteries (Figure 4)—as well as their genetic (Figure 5) and anatomical networks (Figure 6) are significantly different as

well, and moreover this applies not only to the adult stage but also to early ontogenetic stages. Taking into account the information now available, one crucial question emerges: the apparent contradictions between the fin-fold and gill-arch theories and the existing paleontological, developmental and comparative data, could they be due to a true dual origin of the pectoral appendage, combining these theories?

Specifically, developmentally and evolutionary, can the pectoral girdle be mainly related to the head—as proposed by Gegenbaur and recently suggested by authors such as Nagashima et al⁵³ (see Figure 7), Diogo and colleagues,^{11–31} or Gillis and colleagues^{6,52}—and the pectoral fin be mainly associated with the trunk, as postulated by the fin-fold theory accepted by many other researchers? If this is so, and if the pelvic appendage would be mainly related to the trunk—as currently defended by most researchers, including Nagashima et al⁵³ and Diogo and colleagues,¹¹ then (a) the pectoral and pelvic girdles would not be serial homologues; (b) the pectoral and pelvic fins could be “developmental” serial homologues; and (c) this would therefore mean that there could be a partial “developmental” serial homology between the pectoral and pelvic appendages as a whole.

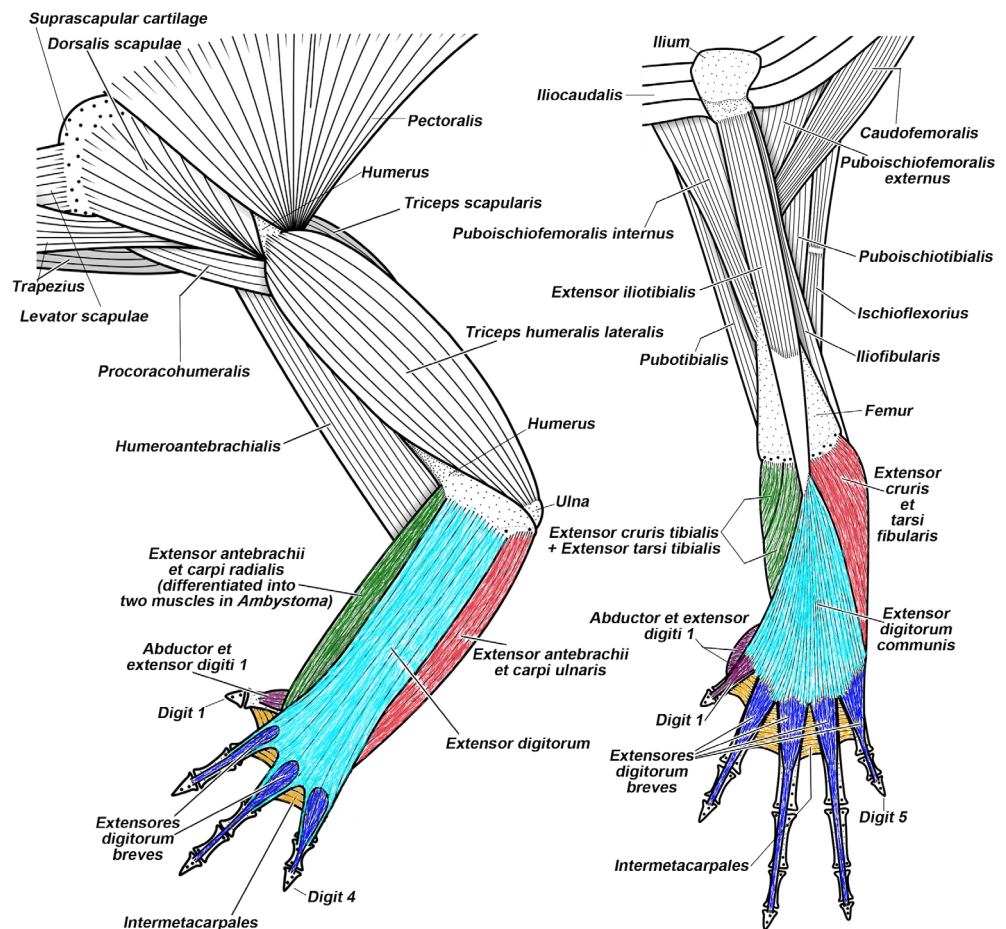


FIGURE 3 Superficial musculature of the forelimb (on the left) and the hindlimb (on the right) of the salamander *Taricha torosa*, seen in dorsal view. Striking similarities between forearm-hand muscles and leg-foot muscles (shown by using similar colors), as well as striking differences between the pectoral-arm muscles and the pelvic-thigh muscles, are evident in most tetrapods (modified from Diogo et al¹¹)

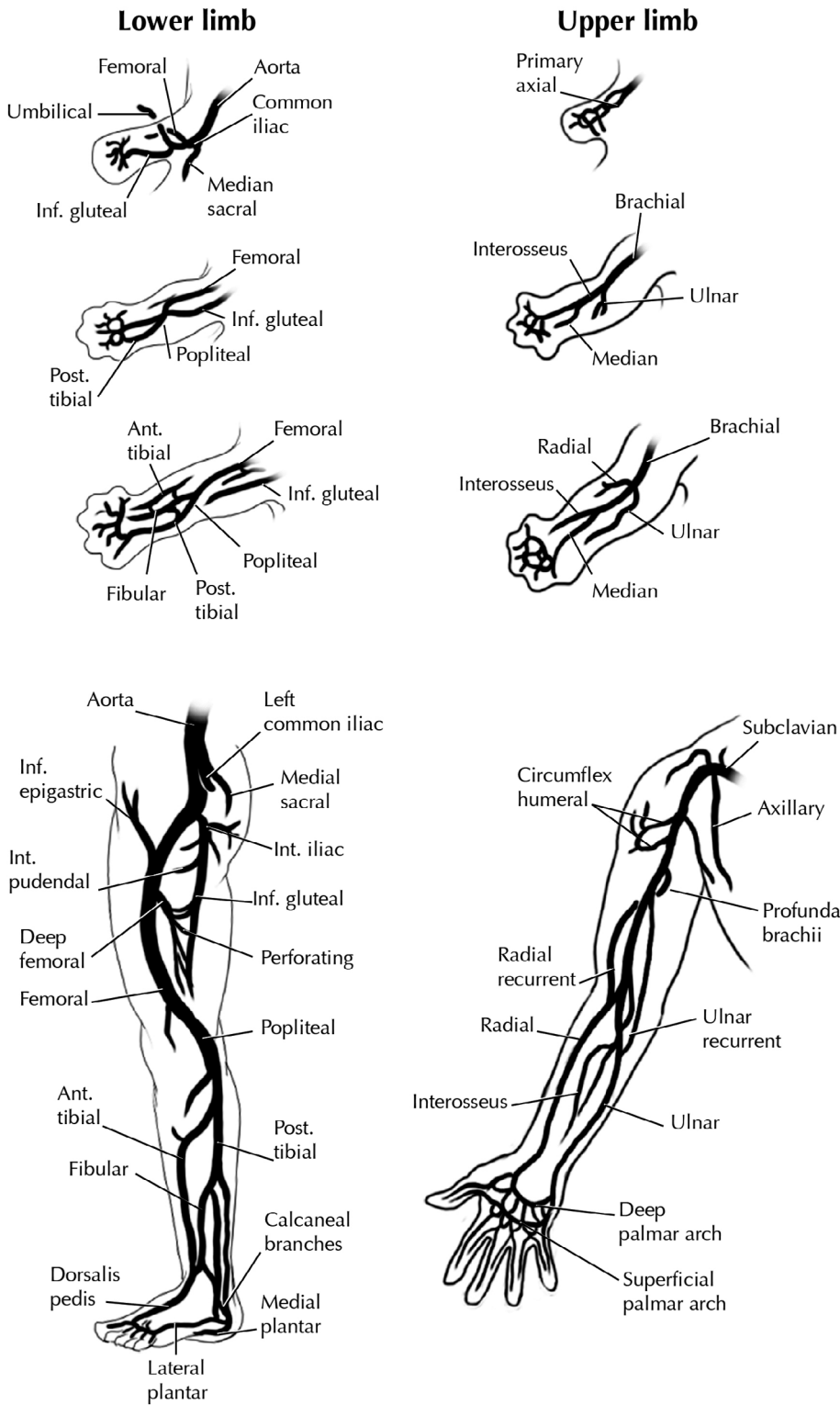


FIGURE 4 Major differences in the region of the pectoral vs pelvic girdles are also seen in other structures, such as arteries, not only in adults but also from the earliest stages of development (modified from Hinchliffe and Johnson¹⁰⁴)

Fascinatingly, in a way this would be similar to what Owen had already suggested, more than 170 years ago: that the pectoral and pelvic girdles are mainly related to the head and trunk, respectively. In fact, as it will be discussed below, Owen argued—as Gegenbaur did—that the pectoral girdle was mainly the result of a transformation of the main bones of a branchial arch, but contrary

to Gegenbaur he did not see the pelvic girdle as a structure also originated from a branchial arch.

The main aim of the present work is therefore to provide a brief review of some of the major arguments in favor of the fin-fold theory, of the gill-arch theory, and of an hybrid between the two theories, in order to better understand the origin and evolution of the pectoral and

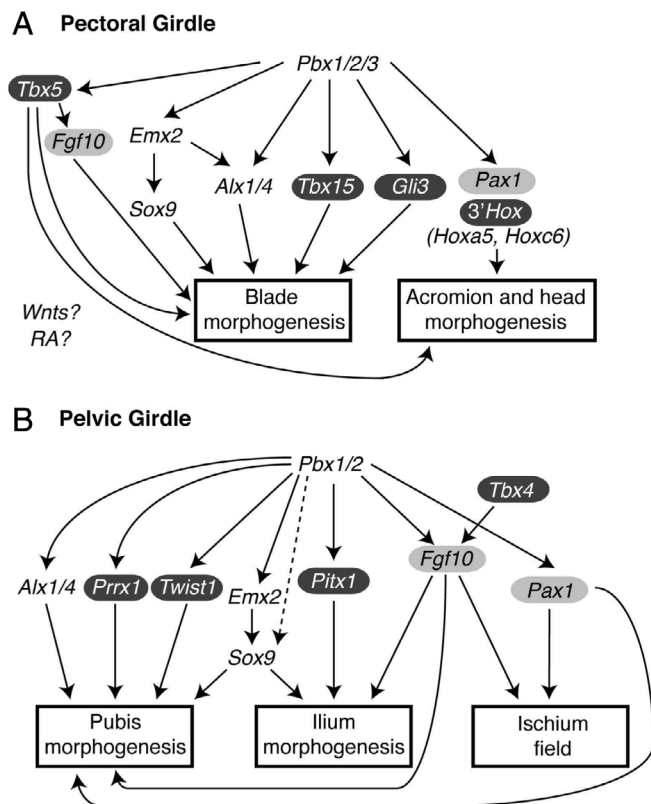


FIGURE 5 Assembled gene networks for pectoral, A, and pelvic, B, girdle patterning (and possibly initiation) in mice (for sources see text). Arrows indicate promoting or repressive interactions among genes, which may be direct or indirect. Genes in black text with no shading are present and have similar functions in both networks (40% of genes), genes in black text with grey shading are present in both networks but may have different roles (20% of genes), and genes in white text with dark shading are present in only one network (40% of genes) (modified from Sears et al⁸⁶)

pelvic appendages, which are crucial topics for comparative anatomy, developmental biology, Evo-Devo, and chordate evolutionary biology in general.

2 | SUPPORT FOR FIN-FOLD THEORY VS FOR GEGENBAUR'S THEORY

The fin-fold theory mainly argues, in more modern terms, that both the pectoral and pelvic appendages evolved from continuous stripes of competency for appendage formation located ventrally and laterally along the embryonic flank.^{54,55} An extension of this theory is that paired appendages evolved with a shift in the zone of competency to the lateral plate mesoderm in combination with the formation of the lateral somatic frontier, therefore enabling the formation of the limb/fin buds with endoskeletons.⁵³

The typical lines of evidence often given to support the fin-fold theory are usually repeated over and over in the literature, including both in specialized papers and summarized in more general textbooks, therefore I will not repeat in detail all these lines of evidence here, because in the present article I am not contradicting this theory: I am instead arguing that it is, indeed, partially correct. An example of a textbook that does a good work in summarizing these lines of evidence is that of Kardong.⁵⁶ As pointed out by this author, some of them come from experimental works on model organisms such as chicken, mice, or sharks. For instance, in tetrapods the body of the embryo is compartmentalized regarding the dorsoventral axis: *Engrailed-1* gene expression is limited to the ventral portion. Within this ventral expression zone *T-box* genes *Tbx5* and *Tbx4* help determine the identity of the pectoral and pelvic appendages, respectively. Sharks also have these two *T-box* genes specifying pectoral and pelvic fins, while the non-vertebrate chordate amphioxus has only one, *AmphiTbx4/5*.⁵⁶ According to Kardong, these data suggest that the hypothetical vertebrate ancestor had lateral fin-folds with *T-box* genes expressed within the *Engrailed-1* domain along the ventral compartment of the body. Then, in the common ancestor of living gnathostomes, duplication of the *Tbx* cluster produced two sets of genes, one anterior (*Tbx5*) and one posterior (*Tbx4*), expressing pectoral and pelvic fins, respectively. Subsequently, the acquisition of *Shh* expression established a proximal-distal axis and promoted outgrowth of the fins from the body wall, as is the case in actinopterygian fishes, sarcopterygian fishes, and tetrapods.^{56,57}

Regarding specialized papers, one of the recent works that reviews in more detail the data supporting the fin-fold theory is that of Abe and Ota,⁴ which moreover included data on their own studies of the fascinating twin-tail goldfish. Specifically, they compared the ontogeny of the bifurcated median fin fold in the twin-tail goldfish to that of the apical ectodermal ridge (AER), a specialized epithelial structure crucial for the development of gnathostome paired appendages. They noted that specialized cell shape and gene expression patterns are conserved between the AER and the median fin fold, for instance the fin fold is formed at the bilateral border of the extended *bmp4*-expressing area in the twin-tail goldfish. They reviewed data suggesting that all fins are developed from identical developmental fields, for example, competent stripes extend bilaterally the length of the trunk between the pelvic and pectoral fins and also of the dorsal midline. Interestingly, they proposed that the ontogeny of the bifurcated median fin fold in twin-tail goldfish might involve an increase of the size of the ventral tissues and field, caused by the *chdA* mutation,

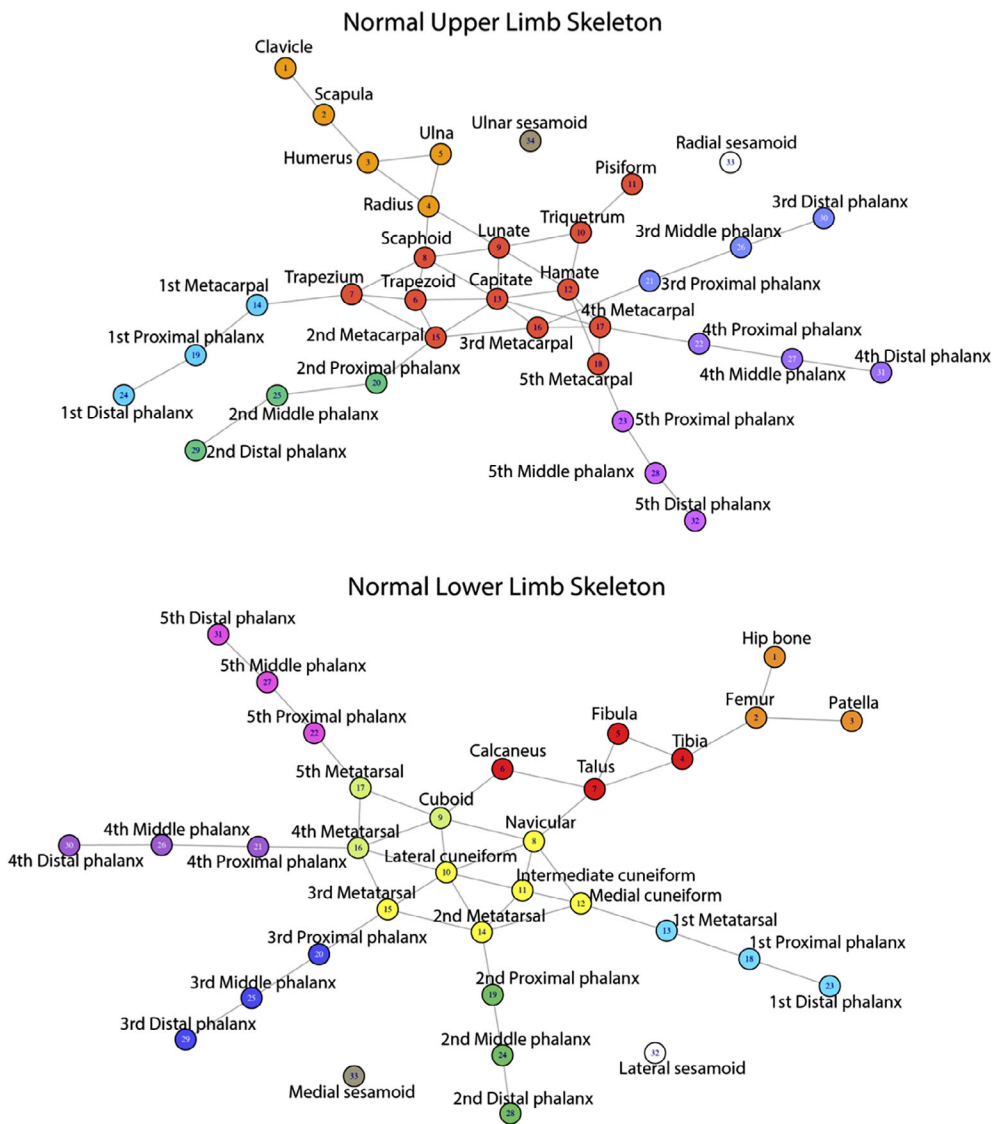


FIGURE 6 Major differences between the anatomical networks of pectoral and pelvic girdle structures are also found, for instance in humans (modified from Diogo et al²⁰)

changing the originally midline-located competent stripe into duplicated paired stripes at pre- and post-cloacal regions, similar to what is seen within the trunk bilateral competent stripes of the paired fins. In fact, it should be noted that there are cases of what clearly seem to be “homeotic transformations” leading to paired hindlimbs in the region of the tail of frogs,^{58,59} in a way somewhat resembling what Abe and Ota⁴ argue about the twin-tail goldfish. Another interesting point, which will be further discussed in “A dual origin of the pectoral appendage?” section, is that the pelvic appendage, more than the pectoral one, is particularly similar to the median fins. Abe and Ota⁴ specifically note that the topological links between the pelvic fin primordia and the pre-anal fin fold suggests that these appendages share very similar developmental mechanisms, for example, in both the wild-type goldfish and twin-tail goldfish the pre-anal fin fold is present at the level at which the primordium of the pelvic

fin appears. Various authors have indeed noted in the past the striking similarities of, for instance, the adult soft tissues of the pelvic fins and the median fins and our recent studies did confirm, and further expanded, the remarkable level and number of these similarities^{24,27,28} (see section below).

In fact, there is only one living taxon where the pectoral fin does have such a striking resemblance with the median fins, the coelacanth *Latimeria*,⁶⁰⁻⁶¹ and such a striking likeness has been argued to be likely due to a homeotic transformation.⁶² However, the simple fact that—even if this mainly only happens in *Latimeria*—an homeotic transformation was likely involved in a phenotype where the adult pectoral fin is so strikingly similar to the pelvic fin and the other fins might in fact be used by those supporting the fin-fold theory. A series of studies in recent decades have indeed confirmed that similar *Hox* patterns do govern the development of the pelvic and

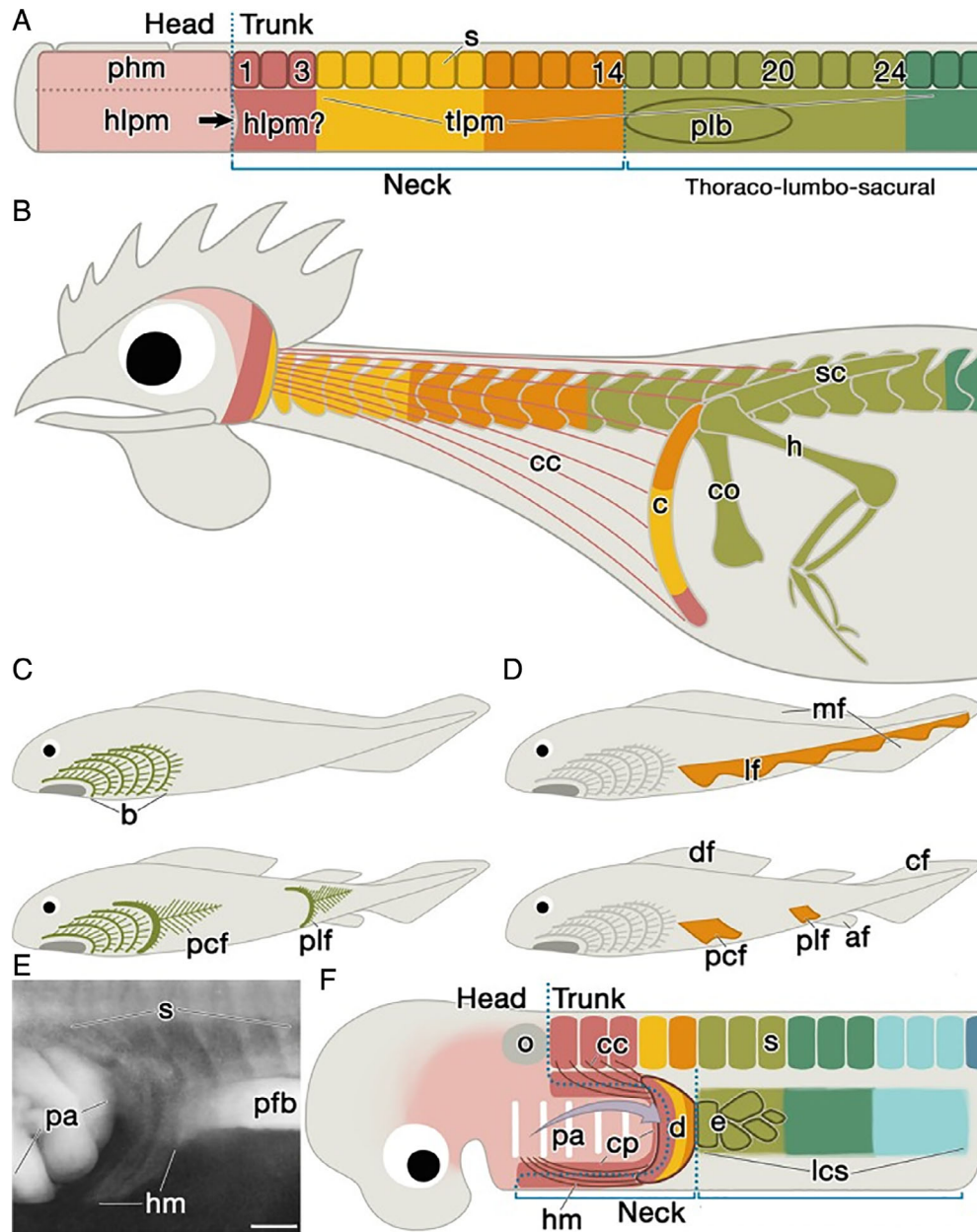


FIGURE 7 Model proposed by Nagashima et al.⁵³ Chickens in early embryonic, A, and adult, B, stages, colors indicating the axial position in the early stage. Whereas paraxial head mesoderm and somites form the axial skeletons, lateral plate mesoderm (LPM) develops into the appendicular skeletons. The embryonic body can be divided into head and trunk regions, and the latter further into the limb-incompetent neck region and the limb-competent thoraco-lumbo-sacral region. The pectoral limb bud (plb) develops at the rostral margin of the thoraco-lumbo-sacral region. C,D, Classic theories on the evolution of paired appendages, the gill-arch theory of Gegenbaur, C, posits that the appendage is made up of the transformed posterior branchial arches, the pelvic fins (plf) being assumed to have migrated caudally; the lateral fin-fold theory, D, posits that the ancestral animal possessed a paired lateral fin-fold (lf) along the length of the trunk, and the structure divided rostrocaudally to form both pectoral (pcf) and pelvic appendages. E, The circumpharyngeal ridge in the *Scyliorhinus torazame* embryo: the hypobranchial muscle anlagen (hm) grow ventrorostrally between the pharyngeal arches (pa) and the pectoral fin bud (pfb); Rostral is to the left. F, Schematic drawing showing the embryonic architecture of the neck region in late embryonic stage. The head LPM expands caudally to form the pharyngeal arches (arrow in A), as a result, the neck region contains the presumptive clavicle domain, the caudal pharyngeal arches, and the horseshoe-shaped circumpharyngeal ridge (cp) as their border. In the CP ridge, the caudal margin of the cephalic neural crest cells and LPM adjacent to the most rostral somites overlap. From the pharyngeal arches, the parathyroid glands develop in tetrapods and the internal gill buds in fishes. In the CP ridge, the cucullaris and hypobranchial muscles develop (viz. circumpharyngeal muscles). The dermal shoulder girdle, D, includes the CP ridge, and forms the caudal wall of the branchial chamber. The endochondral pectoral appendage, E, develops only in the rostral margin of the lateral competence stripe (lcs), which adjoins the presumptive dermal girdle. The arrow indicates growth of the second pharyngeal arch, which develops into the operculum in fishes and the platysma muscle in amniotes. Abbreviations: af, anal fin; cf, caudal fin; df, dorsal fin; mf, medial fin-fold; o, otic vesicle (modified from Nagashima et al.⁵³)

pectoral as well as the medial fins of gnathostomes such as sharks.³⁴ Even in lampreys, the ontogeny of medial fins involves *Hox* genes, indicating that paired appendages originated with the redeployment of median fin gene expression patterns in lateral plate mesoderm.³⁴ Moreover, various studies, either done many decades ago or more recently using state-of-the-art techniques, clearly show that in chondrichthyans such as sharks and batoids at early developmental stages there is an almost continuous, apparently serial, number of nerves and muscle bundles extending to both the hypaxial region and pectoral and pelvic fins in a configuration that does seem to support the fin-fold theory.⁶³

Accordingly, in the last years various authors have postulated evolutionary models based on/supporting the fin-fold theory. For instance, Nuno de la Rosa et al,⁶⁴ based on a developmental analysis focused on tissues and processes, proposed a model to explain the dorsoventral and anterior-posterior placement of paired appendage initiation sites. For them, the number and position of these appendages are the result of a commonality of embryonic tissue environments determined by global interactions involving the somatic and visceral layers of lateral plate mesoderm within the embryonic dorsoventral and anterior-posterior portion of the body. Within this scenario, when what they call the “the lateral mesodermal divide (LMD)” results in a certain tissue environment, fin bud initiation can occur. For instance, the influence of the developing gut represses limb initiation within the midgut region and the ventral body wall—an “endodermal predominance”, that is, the development of the gut, linked with the associated changes to the LMD in gnathostomes, might had resulted in the origin of paired fins. Similarly, Tulenko et al⁶⁵ proposed that a persistent somatopleure arose continuously within the flank from the branchial region to the cloaca, with this novel lateral plate mesoderm domain possibly having carried an *Hox* code shared with the regionalized gut, foreshadowing the localization and differentiation of pelvic and pectoral. However, as they explained, while such a model might be used for defenders of the fin-fold theory, it does not necessitate the presence of a continuous lateral fin fold per se. Or, alternatively the somatopleure may have originally persisted in proximity to the branchial region to establish a pectoral level and subsequently extended posteriorly to the pelvic level, what could be used to actually support Gegenbaur's gill arch theory.

This example shows us that it is not easy at all to separate the data that seemingly support the fin-fold theory vs Gegenbaur's theory, because often the data actually support both. This might indeed be an indication that perhaps the reality is that both theories are partially correct, as argued in the present article. For instance, studies

showing any kind of developmental or adult phenotypical similarities between the pectoral and pelvic appendages, or arguing that it is possible to experimentally homeotically change one of these appendages into the other (see “A dual origin of the pectoral appendage?” section), obviously would provide support for both the fin-fold and Gegenbaur's theories. This is because, as explained above, both these theories argue that these two types of appendages had a similar origin, either from the fin-fold or from the branchial arches, respectively.

Therefore, which kind of data might support Gegenbaur's theory *and not* the fin-fold theory? A typical example, provided several decades ago, was the report that pelvic fins convert into what seems to be a large gill-like organ during breeding season in males of the lungfish *Lepidosiren paradoxa*.⁶⁶ Other examples concern data from paleontology and functional morphology. For instance, Gudo and Homberger⁶⁷ argue that the pectoral girdle of early gnathostomes, as well as living taxa such as chondrichthyans, is an integral and necessary part of the head and directly related to the movement of the jaws, explaining why only vertebrates with jaws have pectoral girdles. Many authors have in fact noted that there are numerous evolutionary and functional reasons for the deep spatial relation between the skull and pectoral girdle in early gnathostomes: the girdle forms the rear wall of the internal branchial chamber, a shield for the pericardial cavity and a secure insertion for the pectoral fins.^{7,8,68} In particular, the renewed attention that has been given to Gegenbaur's theory in the last years is due to the fact that now we know that the links between the pectoral appendage and the head are not only anatomical and functional: they are also developmental. Namely, the pectoral appendage is profoundly associated to the branchial arches developmentally by using markedly similar developmental mechanisms, including a *Shh*-dependence as seen in living taxa such as chondrichthyans, a commonality also seen in the pelvic appendage.^{6,52}

Moreover, recent developmental studies have shown that the cucullaris and its derivatives (eg, protector pectoralis, trapezius/sternocleidomastoideus), which are key muscles connecting the head and pectoral girdle in early gnathostome fossils such as placoderms⁶⁹ as well as living gnathostomes,¹⁸ are actually head, and namely branchial, muscles that are part of the cardiopharyngeal field.^{19,24,70,71} In fact, these are not the only head muscles that are developmentally part of the branchial muscle and that connect the pectoral girdle to the branchial arches: there are various other branchial muscles that do so, such as the constrictores branchiales and the coracobrachiales.^{30,31} However, it is important to note that the muscles connecting the pectoral appendage and the head are always attached to the pectoral girdle, not

the pectoral fin. This also applies to one of the other strongest lines of evidence supporting Gegenbaur's theory: the fact that in at least some vertebrates, such as mice, neural crests—which are mainly involved in skeleton formation and muscle/tendon attachments in the head but not the trunk—contribute to not only the formation of some parts of the pectoral girdle^{53,68,72} but also at least partially to the attachment of tendons/muscles connecting it to the head.^{24,71} That is, the neural crest cell contribution to formation of the pectoral appendage skeleton, as well as to its attachments to the head, seem to apply only to the pectoral girdle, not to the pectoral fin. These facts might indicate that it is mainly the pectoral girdle, not the pectoral fin, that derives evolutionarily from—and remains anatomically and functionally connected to—the branchial arches, as it is precisely proposed in the section below.

3 | A DUAL ORIGIN OF THE PECTORAL APPENDAGE?

As noted in the Introduction, taking into account the information provided in the text above, and in the literature, can the pectoral girdle be mainly related to the head—as proposed by Gegenbaur and recently suggested by authors such as Nagashima et al⁵³ (see Figure 7), Diogo and colleagues,¹¹⁻³¹ and Gillis and colleagues^{6,52}—and the pectoral fin be mainly associated with the trunk, as postulated by the fin-fold theory accepted by most other authors? Fascinatingly, as also noted above, in a way this would be similar to what Owen had already suggested a long time ago: that the pectoral and pelvic girdles are respectively mainly related to the head and trunk. These mesmerizing historical issues have been revived in the last decades by the impressive work of Schmitt, including his 2004 book *“Histoire d'une question anatomique: la repetition des parties”* that covers in more detail the history of the idea of serial homology, comprising also that supposedly existing between the pectoral and pelvic appendages.⁴³ As it was accurately explained in that book, if one reads the original works of Owen, and in particular his 1855 book *“Principles d'ostéologie comparée,”*⁴⁴ it is clear that Owen did argue—as Gegenbaur did—that the pectoral girdle was mainly the result of a transformation of the main bones of a branchial arch. However, he did not fall into the trap leading to the major problem of Gegenbaur's theory, that is, the need to invoke the highly unlikely prospect that the pelvic girdle also originated from a branchial arch and thus that it was originally connected by muscles and other tissues to the head, before migrating all the way to the posterior region of the body and losing all those connections.

Specifically, Owen⁴⁸ clearly stated that as the “stylohyal” and “ceratohyal”—which are structures of the second, or hyoid, arch—derive from the cranial parietal “vertebra,” the scapula and coracoid—which are structures of the pectoral girdle—derive from the cranial occipital “vertebra,” that is, they were clearly part of the *head*. What did Owen say about the origin of the pelvic girdle? That it had nothing to do with the head: it derived instead from a trunk “vertebra,” which he called “pelvic vertebra,” that is, for him these two girdles had nothing to do with each other originally. Indeed, for him those taxa in which there are anatomical similarities between these girdles (mainly not “basal” taxa, see Introduction section) just illustrate cases of “analogy,” that is, of derived similarities.

This leads us, again, to the important a priori assumption made by most current works about the “ancestral similarity-derived divergence”—or “polymerism followed by anisomerism”—type of evolution that serial homologues *are expected* to have had. This applies to research being done about the pectoral and pelvic appendages, as most researchers assume a priori that these appendages are serial homologues: this moreover somehow represents a type of circular reasoning (see Diogo et al¹¹). However, studies in the last decades have not only called into question the idea that the pectoral and pelvic appendages, and particularly their girdles, were ancestrally similar: they have also shown that many of the structures of these appendages actually became *more* similar with time,^{11,12,24,26,28} exactly as noted by Owen.

One could of course argue that the fact that the pectoral and pelvic appendages display some differences between each other can be easily explained by researchers following both the gill-arch theory and, in particular, the fin-fold theory, because developmental biologists have shown that “serial” structures that are patterned in different regions of the antero-posterior axis of the body can indeed have *some* morphological differences.⁷³ That is why this would be less a problem for the fin-fold theory, which assumes that the pectoral and pelvic appendages were physically distant from each other *from the start*, than it would be for the gill-arch theory, which assumes that they both originated from head branchial arches and only then the pelvic appendage migrated posteriorly. But even in this latter case one could argue that since the moment the pelvic girdle started to be more consistently fixed posteriorly, as is the case in the vast majority of living gnathostome adults and embryos, then by being patterned in a posterior region from early development it could share—secondarily—some developmental mechanisms with the trunk that would explain *some* differences between it and the pectoral appendage.

However, first, what is striking is that there are two completely different outlines: one of complete, or almost complete, anatomical dissimilarity between the pelvic and pectoral girdles; the other of striking similarity, regarding nongirdle (or distal) regions of the paired appendages, that is, between the pectoral and pelvic fins of non-basal fish and in particular between the arm-forearm-hand and thigh-leg-foot of tetrapods (Figure 3). Moreover, we know that in very few cases within the pectoral and pelvic girdles and their soft tissues—which mainly always remain different—and in several cases within these nongirdle regions of the pectoral and pelvic appendages, there are striking cases of *derived* similarity, that is, of evolutionary parallelism and thus of historical/evolutionary homoplasy, as stated by Lankaster.^{11,43} For instance, while the structures of the pectoral and pelvic girdles essentially remain different within tetrapod evolution, the overall anatomical similarity between the muscles of the non-girdle regions of the fore- vs the hindlimb is higher in primates such as humans than in taxa such as mice and lizards and than what has been phylogenetically reconstructed for the last common ancestors of extant mammals, and of extant amniotes.^{11,12} There are in fact many clear empirical cases of how forelimb and hindlimb muscles that are strikingly similar to each other in our species were actually acquired relatively recently in our evolutionary history, and strikingly often from very different muscle primordia and/or at very different geological eras, likely due to functional and/or topological constraints exactly as postulated by Lankaster (for details about such cases, see Diogo et al¹¹). These facts have lead Diogo and colleagues¹¹⁻³¹ to suggest that the pelvic and pectoral appendages of vertebrates are *not* evolutionary serial homologues, because they contradict the crucial assumptions of *shared history*—they were not acquired at the same time in vertebrate evolution—and of “ancestral similarity/derived divergence.”

These ideas have been supported by various developmental works in the last decades. For instance, Duboule et al⁷⁴ argued that, developmentally, there is in fact an “older,” proximal region—which is the one in which the pectoral-pelvic appendages always remained more different anatomically as shown by Diogo et al¹¹—and a “newer” region—which is the one in which the pectoral-pelvic appendages became so similar in derived taxa—in the tetrapod limbs. Namely, Duboule et al proposed (p. 135) that the “early collinear activation in the limbs was recruited from the trunk mechanism, allowing for the distal growth of an ancestral appendage up to the wrist area; subsequently, a second global regulation evolved, also located outside the cluster, which was necessary to accompany the emergence of the autopods (hands and feet).” They further noted that “the existence

of distinct regulatory processes for the two waves of *Hoxd* activation in limbs is coherent with the proposal that the proximal and distal parts of our limbs have different phylogenetic histories,” exactly as proposed by Diogo et al.¹¹ Specifically, they argued that mechanisms similar to those implemented during the ontogeny of the trunk may control the early and proximal *Hoxd* gene expression to build the “ancient” proximal part, while “an apparently newly evolved enhancer accompanied the emergence of digits, that is, of a rather recent evolutionary novelty.”

Even if the pectoral and pelvic appendages were more similar—as recently suggested by Trinajstić et al⁷⁵—in some of the earlier fishes having *both* these appendages than it was in the antiarch *Parayunnanolepis* described by Zhu et al,²⁹ there are important points that need to be made. First, even if this would be so, and despite the fact that in placoderms, including *Parayunnanolepis*, both girdles do have a dermal component, the fossil record clearly shows that in the overall, in the *vast majority* of early fishes (eg, placoderms, “acanthodians,” etc) that did have both pectoral and pelvic appendages, these appendages were actually quite different anatomically from each other, particularly their girdle components, as noted above.^{7,8,54,76} For instance, as stated by Coates and Cohn (8:678), “pelvic fins therefore neither originate as simple copies, nor as identical serial homologues of the pectorals—patterns of primitive fin phylogeny therefore provide little evidence of parallel (or concerted) evolution between pectoral and pelvic appendages—close similarity between pectoral and pelvic fins is therefore a specialized feature which is developed most clearly within sarcopterygian (lobe-finned) osteichthyans.” This was also pointed out by Janvier and colleagues, who stated that the pelvic appendages of gnathostomes likely had a “rather different history” that the pectoral appendages did.^{77,78} That is, such a historically early similarity as that suggested by Trinajstić and colleagues would be the exception and not the rule, specially concerning the pelvic and pectoral girdles.

Second, even in those few cases in which there would be a similarity of some structures of the pectoral and pelvic appendages within early fishes, such a similarity would anyway not match at all the strikingly high number of bones and muscles that are so markedly similar in the forelimbs vs hindlimbs of highly derived taxa such as humans (Figure 3). Simply put, in terms of the number of bones and muscles that have clear anatomical correspondents in the other appendage, no fish can match what is seen in humans, or in salamanders¹¹ (Figure 2). That is why Gillis and Hall⁶ were right when they recently stated that *because* both the fin-fold and gill-arch theories are contradicted by purely paleontological and anatomical data, what lead to most researchers starting to be more

receptive, decades ago, to the fin-fold theory was the results of developmental works such as those cited in the “Support for fin-fold theory vs for Gegenbaur’s theory” section above.

However, as discussed in that section, some other key developmental works, such as those of Gillis and colleagues,^{6,52} started to revive at least some parts of Gegenbaur’s theory. Moreover, apart from those developmental works discussed in that section supporting, or at least partially supporting, Gegenbaur’s theory, it is important to emphasize that many *other* developmental works actually contradict crucial parts of both that theory and the fin-fold theory. A subset of them concern works that show that the trend seen in adults—that is, pelvic and pectoral girdles and their structures being essentially anatomically remarkably different from each other, in most member of all major gnathostome taxa—is also seen from the very early stages of development on. This has been clearly shown in studies of skeletal and/or muscle development in sharks,³¹ bony fishes,^{27,28} salamanders,¹⁵ frogs,¹⁷ and humans.^{25,79,80} Similar observations have made by other authors, for example, Cohn et al⁸¹ stated that the pelvic and pectoral appendages of fishes differ markedly in their embryonic development, that is, the radials of the pelvic ones arise from the beginning as separate rods, whereas those of the pectoral ones appear later, by subdivision of a single cartilage disk.

Similarly, Mabee and Noordsy,⁸² in a detailed study of the development of the fins of the paddlefish *Polyodon spathula*, concluded that the resemblance between the pelvic fin basipterygium/metapterygium and the pectoral fin metapterygium is mainly superficial, because the development process by which they are formed is quite different. According to them, in the pectoral fin the metapterygium is segmented off of the scapulocoracoid, without consolidation or fusion of the radials (see also⁸³). In turn, within the pelvic fin individual rod-like basipterygial elements form in a close one-to-one correspondence with the middle radials. Interestingly, once again, they propose a developmental link between the pelvic fin and the medial fins, therefore partially supporting the fin-fold theory. Namely, they state that the appearance of series of individual cartilage rods that might fuse to create skeletal elements with a branching configuration closely associates the pelvic fin with the dorsal and anal fins. In contrast, the pectoral fin and its patterning mechanism involving the breaking up of initially continuous cartilage plates appears to differ significantly from all those fins.

Decades before, Danforth⁸⁴ had made similar observations about the striking differences regarding the formation of the cartilages of the pectoral vs pelvic fins of *Polyodon*, and in addition had noted that such differences

also concerned soft tissues such as muscles. Namely, he noted that the pelvic fin musculature, with superficial and deep adductors and/or adductors, is particularly similar to that of the medial fins. Our recent works on both the development and adult configuration of the musculature of the appendages of several groups of fishes has strongly supported the idea that the pelvic appendage is in general much more similar to median appendages than is the pectoral appendage, in particular its proximal portion.^{24,27,28}

Moreover, the differences between the pectoral and pelvic appendages do not apply only to bones and muscles: they apply also to the development of soft tissues such as nerves and blood vessels, associated with the structures—or lying in the region—of the pectoral and pelvic girdles (see, for example, Figure 4). In fact, the profound differences between the pectoral and pelvic girdle seem to be present at all levels and in all types of tissues, being likely related to deep developmental differences between these girdles. For instance, authors such as Piekarski and Olsson⁸⁵ argued that while in tetrapods there is in general at least some type of somitic contribution to the pectoral girdle, at least for chicken and mice detailed labeling has shown that there is no somitic contribution to the pelvic girdle. In fact, in a broad review done by Wilson et al,³² in which they summarized data available for various early vertebrate groups, they specifically stated that pectoral and pelvic appendages were very different from the beginning of their evolution. Namely, they argue that the pectoral appendages have a developmental precursor that seems to be more dorsal and “postbranchial”—thus partially supporting Gegenbaur’s ideas. In turn, they argue that the pelvic appendages have a precursor that seems to be more ventral, almost lying on the ventral midline in some cases, thus resembling the median appendages—therefore partially supporting the fin-fold theory.

Furthermore, these differences between the pectoral and pelvic appendages do not apply only to comparative developmental anatomy or to general developmental mechanisms, but also to genes and to both genetic and anatomical networks. As pointed out by Sears et al,⁸⁶ recent embryological and genetic data suggest that the anatomical similarity between the fore- and hindlimbs arose through the sequential, *derived* deployment of similar developmental programs and gene networks, thus not being due to ancestral/evolutionary serial homology. However, as they pointed out, much less was known about the developmental differences/similarities of the pelvic vs pectoral girdles. They therefore provided the first detailed review of the developmental programs and gene networks of these girdles, and showed that these programs and networks display fewer similarities

between the pelvic and pectoral girdles than between the non-girdle regions of the tetrapod fore- and hindlimbs (Figure 5). For example, they identified 10 genes with a role in pectoral girdle development that could be placed in the network of this girdle, and 10 genes for the pelvic girdle network: fewer than half (4/10) of the pectoral girdle network genes are also present in the pelvic girdle network. In contrast, the networks regulating initial specification and outgrowth of the forelimb and hindlimb share about, or more than, half of their genes (3/5 for forelimb; 3/6 for hindlimb), whereas the networks regulating later stages of forelimb and hindlimb outgrowth and patterning share almost all of their genes (27/28 for forelimb; 27/29 for hindlimb). They therefore concluded that the “available data therefore support recent hypotheses that the anatomical similarities between the fore- and hindlimbs arose during the fin-to-limb transition through the derived co-option of similar developmental mechanisms, while the phylogenetically older pectoral and pelvic girdles have remained more distinct” (⁸⁶:2543).

This accords with what other authors had previously proposed, that is, that similar genes were *secondarily* co-opted for the development of the hindlimb and forelimb, respectively—“gene piracy,” for example, *Tbx4* and *Tbx5*—during the fish-tetrapod transition.^{11,87,88} These developmental and molecular data indeed help to explain, mechanistically, why we do actually see a trend towards more anatomical similarity between the pectoral and pelvic appendages *as a whole*—essentially with their distal, non-girdle regions becoming more similar while the girdles themselves mainly remain as dissimilar as they were ancestrally, as noted above. Importantly, the very same patterns are also seen when one studies the anatomical networks of the pectoral vs pelvic appendage: a striking dissimilarity between the girdles and a higher similarity between the distal, non-girdle structures (Figure 6). Likewise, studies of the patterns of morphological integration in the appendicular skeleton of mammals show that the pectoral and pelvic girdles are much less integrated than are any other portions of the pectoral and pelvic appendages, and that the pectoral and pelvic stylopods are also less integrated than the zeugopods,⁸⁹ precisely as predicted by Diogo et al.¹¹ Moreover, such studies also show that specialized taxa/limbs have pectoral and pelvic appendages that are more integrated than they are in less specialized/more plesiomorphic cases, exactly as also predicted by Diogo et al.¹¹ and by Owen,⁴⁷ who argued that the appendages are particularly similar to each other in derived taxa such as bats, horses and plesiosaurs (see above). This is indeed a remarkable case of consistency between the results of paleontological, functional, developmental, evolutionary, genetic, gross anatomical, integration, and anatomical network studies (Figures 3-6).

Furthermore, a series of other recent developmental studies have also helped to understand why instead of derived divergence between the pectoral and pelvic appendages as whole, as most researchers would assume a priori, the tendency appears to be *independent/parallel* acquisition of various types of appendages at different times of history in several vertebrate clades. This is exemplified by the very complex taxonomic distribution of not only the pectoral and pelvic appendages, as explained above, but also of other paired structures, such as reproductive organs and “anal” fins in the stem of gnathostomes.⁹⁰⁻⁹³ Co-options of gene expression probably explain the homoplastic acquisition of these and other structures: patterns of *Hox* and *Shh* expression are indeed similar in structures as diverse as the head barbels of paddlefishes, the sexual claspers of sharks, and the vent—a medial structure analogous to the urethra—of some fishes.⁹⁴ As noted above, similar *Hox* patterns are also involved in the ontogeny of the pelvic and pectoral, and of the median, appendages of sharks.³⁴ Therefore, if one would argue that the sharing of such developmental mechanisms by the pectoral and pelvic appendages—in particular for the development of their non-girdle structures—necessarily means they are “developmental serial homologues,” then one should also consider them to be “developmental serial homologues” of head barbels or sexual claspers. Basically, each and every prominence of the body would need to be considered a “developmental serial homologue,” because there seems to be no way of forming such prominences without co-opting at least some similar gene expression patterns.

This leads us to the case-studies involving homeotic transformations, which are one of the major arguments in favor of such an assumption that the term “developmental serial homologues” can apply to the pectoral and pelvic appendages as *a whole* and that therefore these appendages were likely ancestrally anatomically similar. That is, that we can in theory talk about a single “paired appendage” standard, ancestral model, from which both the pectoral and pelvic appendages arose, an idea that shows how the influence of the romantic idea of an ideal “archetype” and of the repetition of “basal” forms is still so much imbedded in our current way of thinking. However, the reality is that within all the cases given in the literature to support so-called “experimental homeotic transformations” of pelvic appendages into pectoral appendages, or vice-versa, a detailed anatomical analysis clearly reveals that there are huge morphological differences between the “produced” and normal phenotypes. Moreover, as noted in the section above, similar cases of so-called “homeotic transformations” have been also described between for instance the tail and the hindlimb of frogs, but the authors of those descriptions did

obviously not argue that such cases show that the tail and hindlimb are necessarily direct serial homologues or that there is a “default tail/hindlimb ancestral appendage.”^{57,58}

I plan to write a detailed paper focusing on the striking differences between the normal phenotype of a limb and what is truly obtained in experimental studies with *Tbx4*, *Tbx5*, and/or *Pitx1*, as some of the more pertinent conclusions of those studies are often accepted by the scientific community without such a detailed anatomical analysis. Therefore, here I will just provide a few examples of such differences, without of course wanting to criticize any specific study or authors, particularly because I understand that most authors of such papers are not anatomists. For instance, in Ouimette et al⁵⁸ paper “Divergent transcriptional activities determine limb identity,” it is stated that introduction of *Tbx5* in *Pitx1*^{-/-} mice hindlimbs produced one novel skeletal transformation reminiscent of a forelimb-specific feature. Namely, they argue that the angle of the pelvic girdle relative to the vertebral column (spine) in *Tbx5* mutants is greater than normal pelvic girdles, being reminiscent of the scapula/spine angle. However, when one examines in detail the anatomy of the structure shown in the picture they refer to—column 4 of their Figure 2B, that structure does not resemble at all a normal mouse scapula. Actually, the authors recognize this fact, subsequently, when they state that the ability of *Tbx5* to direct the appearance of forelimb features in the hindlimb may be *limited* by the assay as it relies on expression at an ectopic site.

However, these important nuances, recognized by the authors themselves, are unfortunately lost when many researchers cite such studies as examples of cases showing how a hindlimb can be “homeotically transformed” into a forelimb. In reality, to my knowledge, none of these studies have actually produced anything that does truly resemble a forelimb. The differences between the limb that is supposed to have been “produced” and the phenotype that was actually produced are particularly striking when one analyses soft tissues such as muscles. For instance, Ouimette et al⁹⁵ state that in their *Pitx1*^{-/-} mutants the tibialis anterior muscle is split into two muscles, similar to the division of the topologically similar muscle of the forelimb, the extensor carpi radialis, into the brevis and longus muscles in mice and other mammals. However, while it is true that a few transformations can have something to do with specific features seen in the normal forelimb, the overall musculature of the supposed “forelimb” obtained in such *Pitx1*^{-/-} mutants is still very different from that of a normal mouse forelimb. For instance, in the produced limb there are still two lateral (fibular) muscles, as is the case in the normal mouse hindlimb, instead of a single lateral

muscle as seen in the normal mouse forelimb (the extensor carpi ulnaris).

To give just one more example regarding mice, I will refer to a subsequent study by Duboc and Logan,⁹⁶ showing tendons and muscles of mouse *Pitx1*^{-/-} hindlimbs and normal forelimbs in impressive detail. When one does a comprehensive, deep anatomical analysis of such details, it becomes even more clear how the *Pitx1*^{-/-} hindlimbs are in fact strikingly different from normal forelimbs. For instance, the muscles and tendons of the *Pitx1*^{-/-} hindlimbs shown in their Figure 3 are overall much more similar to normal hindlimb muscles than to normal forelimb ones. They have short muscles such as the flexor digitorum brevis (in contrast to the long flexor digitorum superficialis of the forelimb), as well as an overall proximo-distal orientation of all the muscles, as often seen in the hindlimb, while in the forelimb there is also a marked radio-ulnar orientation of the muscles. Also, in *Pitx1*^{-/-} hindlimbs there are two muscles (fibularis quinti and fibularis quarti) to digits 5 and 4, respectively, as normally happens in the hindlimb, while in normal mouse forelimbs there is usually a single muscle extensor digiti minimi with a distally bifurcated tendon to digits 4 and 5. In fact, the authors themselves recognize, once again, that the *Pitx1*^{-/-} hindlimbs are very different, in general, from normal forelimbs, and even argue that one possibility to explain the very few soft tissue similarities is that such similarities are secondarily caused by epigenetic events caused by the changed bone configuration. Specifically, they state that their results are not able to distinguish whether the absence of some “typical hindlimb muscles” in *Pitx1*^{-/-} hindlimbs is secondary to the loss of the bone insertion site in those hindlimbs or instead a primary defect in the nascent muscle bundles. The possibility that what might seem to be soft tissue similarities between *Pitx1*^{-/-} hindlimbs and normal forelimbs is more related to secondary epigenetic events than to the existence of a true “original default limb-type” is reinforced by the fact that recent studies have shown that the configuration of limb muscles and tendons is indeed often related to the presence and topology of the surrounding skeletal elements.^{21,22,97} In fact, in their page 5308, Duboc and Logan⁹⁶ clearly recognize that “neither the forelimb nor the hindlimb represents a default limb-type—forelimb and hindlimb morphologies are derived states, in part, reflecting their divergent evolutionary histories and the influence of different selection pressures.”

It is important to stress that this does not apply only to mice, or to mammals. Similar studies have been done with other tetrapods, with the same striking differences between the mutant limb and the normal phenotype of the limb to which it has supposedly been “produced.”

For instance, Domyan et al.⁹⁸ show how feathered feet in pigeons and chicken are produced from a “partial transformation” from hindlimb to forelimb identity mediated by *cis*-regulatory changes in *Pitx1* and *Tbx5*. However, to use the term “partial transformation” seems to be exaggerated in this context, because apart from having some feathers, the skeletal and muscular structures of the produced limbs are completely different from those of typical bird wings. In fact, they later recognize that there are actually profound differences, exactly as the authors of the papers discussed just above did. Namely, they specifically state that what their results truly show is that limb-type identity is very likely not a simple binary choice between two global fates. For instance, they recognize that the feather-footed pigeons have a transformation of the distal hindlimb dermis but other hindlimb mesoderm derivatives such as muscles and the skeleton show mainly no wing-like similarities at all. Actually, what a detailed review of the results of such experimental studies indicates is very much in line with the main hypothesis of the present work. That is, that there are *some* resemblances and shared developmental mechanisms between the forelimb and hindlimb *sensu stricto*, likely reflecting the fact that the pectoral and pelvic fins evolved by the co-option of mechanisms involved in the formation of median fins. However, such resemblances are not as marked as they are often assumed to be and, importantly, do not seem to apply at all, or apply only to a very minor extent, to the structures of the pectoral and pelvic *girdles*, likely reflecting the fact that they have very different developmental origins.

Interestingly, although this subject is often neglected (or simply often ignored, for being “controversial”) since at least 40 years ago a few authors did start stressing that the only way to solve the paradox created by the evidence that the pectoral and pelvic girdles are so markedly different while the pectoral and pelvic fins share numerous similarities might be to accept that the *pectoral girdle and fin* have mainly different origins. For instance, Tabin (⁹⁹:293) stated that “according to a controversial view”—that of Zangerl¹⁰⁰, unlike the pectoral fin, the shoulder girdle with which it articulates may have evolved from a modified branchial arch.” As recognized by Tabin, such a hypothesis could indeed help to solve this paradox, and is actually supported by various lines of evidence. According to Tabin, one of these lines of evidence is molecular evidence, which is consistent with this different origin of the pectoral girdle, from a different *Hox* gene, *Hox-3.3*, which is expressed in the anterior portion of the embryonic body wall at the base of the branchial arches. Tabin cites various studies showing that this gene is also specifically expressed in the extreme proximal, anterior region of the forelimb bud, but not the hindlimb

bud, as well as indirect experimental evidence indicating that *Hox-3.3* plays a role in the morphogenesis of the shoulder region.

Another line of evidence for a possible dual origin of the pectoral appendage is paleontological evidence. This is because we know that there are actually fossil taxa with appendicular fins but without appendicular girdles, that is, there is not necessarily a single, indivisible “appendage package” including both a fin and a girdle.¹⁰¹ According to Johanson,¹⁰¹ a dorsal zone of competence for fin development evolved in early vertebrates, including lampreys, such fins being derived from somites (primaxial) and supported by radials. Then, this dorsal zone of competence was duplicated and co-opted to a new ventrolateral position along the flank, including relevant genes and a somitic origin of the fin and musculature, with fins supported by fin radials being developed from this zone of competence that became extended both above and below the gill arches. She argues that a variety of fin-like structures formed within the zone of competence, while the pectoral and pelvic girdles were absent, in this evolutionary stage characterized by the euphaneropids, anaspids, and thelodonts. In this scenario, the origin of the Osteostraci and evolution of a pectoral girdle would indicate that the competency zone has shifted to the lateral plate mesoderm with the evolution of the abaxial region, along with the establishment of the lateral somitic frontier. Be that as it may, the main conclusion of Johanson¹⁰¹ that is particularly crucial for the present work is that the fin or “fin-like” structures characterizing early vertebrates were derived from somites and supported by fin radials, but not by pectoral or pelvic girdles, being therefore similar to dorsal unpaired fins developing in the primaxial region, thus indicating that the girdles are *de novo*, *different* structures.

Such paleontological data are in line with developmental data, such as those referred to by Duboule et al.,⁷⁴ cited above. In fact, apart from proposing that the proximal and autopodal regions of the limbs have different developmental and phylogenetic origins, they also proposed that the girdle portion of the pectoral appendage is developmentally very different from the stylopodial (humeral) and zeugopodial (radius/ulna) portions of the limb, that is, to the part that corresponds to the “phylogenetically old” structures of the pectoral fin of fishes. For instance, they note (p. 135) that if one eliminates *HoxA* and *HoxD* clusters one gets “a runt of a humerus, while the scapula was fully formed: the piece of that is left, the scapula and mid humeral part, is roughly up to the deltoid crest,” corresponding “to the part of the early limb bud that expresses a transcription factor called *Meis1*.” That is why they propose that there is a difference between the morphological and the genetic definitions of

a “forelimb”: for them, developmentally the forelimb proper truly starts at the mid-humeral part, being a kind of a “trunk” extension.

Still another line of evidence for a possible dual origin of the pectoral appendage comes from studies on the innervation of this appendage. For instance, Ma and colleagues compiled embryological and anatomical evidence for actinopterygian fish, cartilaginous fish, and sarcopterygian fish showing that pectoral motoneurons originate in both the spinal cord and the hindbrain, thus supporting “a hindbrain–spinal phenotype as the ancestral vertebrate condition.”¹⁰² This therefore leads us to the most recent and straightforward work about this issue, in which the authors finally directly state what all the data cited in the present article seems to be pointing out: that the pectoral appendage might in fact have a dual origin, the girdle portion being more associated with the head, and the fin/limb proper being more related to the trunk⁵³ (Figure 7). Namely, Nagashima and colleagues⁵³ found, in their developmental work in chicken, that the origin of the clavicle is associated with the head mesoderm between the somite levels 1 to 14. Importantly, the rostral portion of the clavicle-forming region overlaps the primordium of the cucullaris muscle—the head branchial muscle referred to above, embraces the pharyngeal arches caudally, and can be experimentally replaced with head mesoderm to form the cucullaris. They argue that this means that the clavicle has developed at the head/trunk boundary. They then specifically state that, for them, the dermal pectoral girdle of gnathostomes (or at least part of it) represents the wall of the branchial chamber into which the endochondral pectoral appendage became attached to. According to Nagashima, in contrast with the dual girdle-head and fin-trunk origin of the pectoral appendage, the pelvic appendage—that is, including *both* its girdle and fin—is developmentally very likely only part of the trunk (pers. comm.). When one analyzes all the available data, from studies as diverse as those about the development and adult comparative anatomy of the skeletal and soft tissues of the pectoral and pelvic appendages, to works on molecular mechanisms and genetic networks, and on fossils and anatomical networks, one can say that the dual origin proposed by Nagashima et al,⁵³ schematized in Figure 7, is in fact the one that better fits the overall evidence gathered so far.

The purpose of the present article was precisely to show that, when we interpret the developmental works of authors such as Nagashima et al⁵³ within a broader framework, including comparative, paleontological, genetic and networks data, one can finally have a much better idea of the evolution of the appendages of vertebrates as a whole, including what seems very likely a truly dual origin of the pectoral appendage. That is, when

one is able to see the elephant as a whole, instead of just focusing in some of its parts (that is, in this case on some separate, more specific studies), one realizes that perhaps all the evidence that was deemed to be “contradictory” within the Gegenbaur and fin-fold theories, was actually pointing out that *both* of them were indeed partially right.

4 | GENERAL REMARKS

There is a long-standing debate between the fin-fold vs gill-arch theories for the origin and evolution of the pectoral and pelvic appendages, with apparent contradictions between the existing paleontological, developmental and comparative data. Therefore, one should at least consider the possibility of a dual origin of the pectoral appendage, with the pectoral girdle being mainly related to the head and the pectoral fin to the trunk. In the present article, I show that the overall analysis of all the data obtained so far does support this idea. Moreover, apart from the direct evidence provided by these data, there is also the question of evolutionary plausibility. It was always almost impossible to explain how Gegenbaur's model could give a plausible explanation for the very posterior position of the pelvic appendage, and particularly its lack of attachments to the structure from which it supposedly had originated from: the head. The evolution of soft tissues is extremely conservative, and structures such as muscles and nerves almost never get completely disconnected from the structures to which they were originally attached, even in extreme cases of morphological changes, as was pointed out in a recent survey of the evolution of the muscles of all major groups of chordates.²⁴ Similarly, the fin-fold model was never successful in explaining how the pectoral girdle got its attachments to various bones—in many taxa—and to so many muscles—in all taxa—that are developmentally clearly part of the head, such as the cucullaris and various other branchial muscles. In fact, as explained above, it is important to note that the muscles connecting the pectoral appendage and the head are always attached to the pectoral girdle, not the pectoral fin, supporting again the idea that it is mainly the pectoral girdle, not the fin, that derives from the branchial arches.

Moreover, neither the fin-fold nor the gill-arch theories could truly explain why the pectoral and pelvic girdles and their muscles have remained, from the very beginning, so different from each other, clearly more different than those of the pectoral and pelvic fins/limbs normally are. Furthermore, as emphasized above, we have direct evidence that such a dual scenario was possible, because there are fossils with paired fins that are not necessarily attached to girdles. That is, the overall

evidence available indicates that (a) the pectoral and pelvic girdles are not serial homologues, as the former mainly originated from the head and the latter from the trunk; (b) however, the term “developmental serial homologues” can possibly be applied to the pectoral and pelvic fins, as they both originated from the trunk, and particularly to the hand and foot of tetrapods, which later co-opted very similar genes and mechanisms for their development; (c) the pectoral and pelvic appendages as a whole could thus potentially be considered “partial serial homologues.” That is, instead of assuming a priori that the pectoral and pelvic appendages as a whole correspond to each other and/or were necessarily similar ancestrally, an unconscious remainder of the very influential romantic ideas of a mainly polysomeric archetype/ancestor, researchers should at least be open to the idea that the pectoral appendage might have a dual origin, and analyze a posteriori all the possible options in face of what their results truly indicate.

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ORCID

Rui Diogo  <https://orcid.org/0000-0002-9008-1910>

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