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DEVELOPMENTAL DYNAMICS 00:000–000, 2015
DOI: 10.1002/DVDY.24336

REVIEW

Evolutionary Developmental Pathology and Anthropology: A New Field Linking Development, Comparative Anatomy, Human Evolution, Morphological Variations and Defects, and Medicine

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We introduce a new subfield of the recently created field of *Evolutionary-Developmental-Anthropology* (Evo-Devo-Anth): *Evolutionary-Developmental-Pathology-and-Anthropology* (Evo-Devo-P'Anth). This subfield combines experimental and developmental studies of nonhuman model organisms, biological anthropology, chordate comparative anatomy and evolution, and the study of normal and pathological human development. Instead of focusing on other organisms to try to better understand human development, evolution, anatomy, and pathology, it places humans as the central case study, i.e., as truly model organism themselves. We summarize the results of our recent Evo-Devo-P'Anth studies and discuss long-standing questions in each of the broader biological fields combined in this subfield, paying special attention to the links between: (1) Human anomalies and variations, nonpentadactyly, homeotic transformations, and "*nearest neighbor*" vs. "*find and seek*" muscle-skeleton associations in limb+facial muscles vs. other head muscles; (2) Developmental constraints, the notion of "phylotypic stage," internalism vs. externalism, and the "*logic of monsters*" vs. "*lack of homeostasis*" views about human birth defects; (3) Human evolution, reversions, atavisms, paedomorphosis, and peromorphosis; (4) *Scala naturae*, Haeckelian recapitulation, von Baer's laws, and parallelism between phylogeny and development, here formally defined as "*Phylo-Devo parallelism*"; and (5) Patau, Edwards, and Down syndrome (trisomies 13, 18, 21), atavisms, apoptosis, heart malformations, and medical implications. *Developmental Dynamics 00:000–000, 2015*. © 2015 Wiley Periodicals, Inc.

Key words: von Baer and Haeckel's recapitulation; atavisms and reversions; nonpentadactyly; logic of monsters; muscle–bone spatial associations; facial muscles; phylotypic stage; constraints; internalism and externalism; Down syndrome and other trisomies

Submitted 18 March 2015; First Decision 10 August 2015; Accepted 12 August 2015; Published online 0 Month 2015

Introduction

The recent rise of evolutionary developmental biology (Evo-Devo) has revived interest in comparative anatomy, particularly of soft-tissues, and of "teratology," now designated as the study of congenital malformations. These are fields that were somewhat "asleep" during many decades after having a prominent role in biological and anatomical works in the 18th, 19th, and beginning of the 20th centuries, with only a few notable authors/works as exceptions in the second half of the 20th century (e.g., Willis,, 1958). In their excellent book "Wonders and the Order of Nature" Daston and Park (1998) provide a remarkable, extensive historical account of the pronounced interest of the scientific community and even the general public, including teologists and artists, about "teratology," particularly between the 12th and 18th centuries. Following the rise of Evo-Devo—and the creation of new subfields such as Evolutionary Developmental Paleontology (Sánchez-Villagra, 2010)—there have been attempts, in recent decades, to investigate human anatomy and birth defects under a more modern evo-devo perspective. These attempts have been fueled especially by advances in molecular and developmental methods (e.g., genomics, transgenics, lineage tracing) and investigations of congenital deformations have thus acquired a more mechanistic underpinning; lacking direct experimental analyses, studies on humans, however, rely mainly on extrapolations, key among which are from anthropological, and pathological analyses (e.g., Galis,, 1999; Leroi, 2003; Verhulst, 2003; Blumberg, 2009; Held, 2009).

We were fortunate to be an active part of a recent effort, initiated by our close colleagues Julia Boughner and Campbell Rolian, to create the new field of *Evolutionary Developmental Anthropology (Evo-Devo-Anth)* (Diogo and Wood, 2015). In particular, our lab is developing a new subfield of Evo-Devo-Anth, which is

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ABBREVIATIONS: LoMo, Logic of monsters; HaRe, Haeckel Recapitulation; voBa, von Baer

Article is online at: http://onlinelibrary.wiley.com/doi/10.1002/dvdy.24336/abstract

designated here as *Evolutionary Developmental Pathology and Anthropology, or Evo-Devo-P'Anth*. Evo-Devo-Anth is based on a combination of experimental/developmental studies of nonhuman model organisms and primate/human evolution, genetics and anatomy, principally concerning hard-tissues (e.g., skeleton/teeth). Our Evo-Devo-P'Anth research includes these lines of research but also pays special attention to data obtained from chordate comparative, developmental, and evolutionary anatomy and from the direct study of normal/abnormal human development (using, e.g., cadaveric collections of hospitals, museums, and other institutions), with a major focus on soft tissues (e.g., muscles) (Diogo et al., in press; Smith et al., 2015a,b).

For this purpose, here we combine the results of our long-term project on chordate comparative anatomy, evolution, and development (e.g., Diogo, 2004a,b, 2005, 2007; Diogo and Abdala, 2007, 2010; Diogo et al., 2008a,b, 2009a,b, 2012b, 2015b), including primates (e.g., Diogo and Wood, 2011, 2012b, 2013; Diogo et al., 2010, 2102a,b, 2013a-d), with our recent work on human ontogeny and birth defects. We hope that this review will disseminate Evo-Devo-Anth and encourage others to do more studies in the line of the Evo-Devo-P'Anth subfield we are developing and/or to include soft-tissues in their studies.

Human anomalies and variations, nonpentadactyly, homeotic transformations, and "*nearest neighbor*" vs. "*find and seek*" muscle-skeleton associations in limb+facial muscles vs. other head muscles

Nonpentadactyly and the specific spatial associations between limb bones and muscles are topics that have long attracted researchers' attention (e.g., Owen, 1849), particularly because nonpentadactyly is the most common human limb birth defect (Castilla et al., 1996). These topics are of particular interest to Evo-Devo because they relate to broader themes such as the occurrence of evolutionary trends, convergence, reversals, and homeotic transformations (i.e., the replacement of a body part by one that normally forms in another region of the body). For instance, in pre-axial polydactyly, a common congenital anomaly of the human hand, thumb duplication leads to the two most radial digits having an homeotic identity of digit 1 (Light, 1922; Heiss, 1957; Castilla et al., 1996). Homeotic transformations also played a crucial role in the evolution of normal phenotypes. It is now usually accepted that the wing digits of adult birds derive from the second, third, and fourth developmental anlages (embryonic condensations; e.g., de Bakker et al., 2013). However, homeotically and morphologically, these digits correspond to digits 1, 2, and 3 of other tetrapods; a similar homeotic transformation seemingly also occurred in the hand of the three-toed Italian skink *Chalcides* (Young et al., 2009). To study the spatial associations between limb bones and muscles, we have recently compared the adult morphology, development, and regeneration of these structures in several wild-type and non–wild-type tetrapods (e.g., Diogo et al., 2013c; Diogo and Tanaka, 2012, 2014; Diogo and Ziermann, 2014; Diogo and Molnar, 2014).

We have also investigated alterations in muscle attachments found in human with congenital nonpentadactyl limbs, and assessed whether these changed patterns are similar to those found in wild-type nonhuman tetrapods with nonpentadactyl limbs (Smith et al., 2015a). We recently described and discussed in detail the results of those works and their medical implications (Diogo et al., 2015a). Therefore, here we only briefly summarize those results and combine them with new data we have recently obtained on head muscle-skeleton associations in cases of severe human congenital malformations, to provide a more integrative context for the discussions provided below. The most important conclusion of those studies was that the nonpentadactyl limbs of wild-type taxa such as frogs, salamanders, crocodilians, chickens, and humans with birth defects exhibit a surprisingly consistent "*nearest neighbor*" pattern: the identity and attachments of the distal fore- and hindlimb muscles seems to be mainly related to the physical (topological) position, and not to the number of the anlage or even to the homeotic identity, of the digits to which the muscles are attached. Here, "topological position" refers to the adult relationship with other structures, and not to the position of the developmental anlagen. For instance, the topological position of the adult avian wing digit derived from the second anlage is digit 1, because this is the most radial adult digit. Therefore, in this case study, the topological position (digit 1) and homeotic identity (digit 1) are the same and are different from the anlage from which the digit develops (the second anlage: e.g., Young et al., 2009). Accordingly, chickens exhibit a consistent "nearest neighbor" pattern in which the abductor pollicis brevis inserts onto this most radial digit; in pentadactyl taxa this muscle is always inserted onto digit 1, which derives from the first, and not the second, anlage (Diogo and Abdala, 2010). The case of chickens is different from the case of salamanders with four hand digits (e.g., axolotls). In axolotls, digit 5 is missing and digit 4 develops from the anlage of digit 4 and has a homeotic identity of digit 4; however, its topological position is similar to that of digit 5 in pentadactyl tetrapods because this is the most ulnar digit. The axolotl case illustrates and corroborates our hypothesis because, although the homeotic identity of this most ulnar digit is that of digit 4, the digit is associated with muscles that normally go to the digit 5 of pentadactyl tetrapods (e.g., abductor digiti minimi: Diogo and Tanaka, 2012a).

Regarding our studies of humans, an illustrating example supporting our "*nearest neighbor*" model concerns a trisomy 18 fetus with a 6-digit hand (partial duplication of thumb) and a 4-digit hand (no thumb). As predicted by our model, the hand with no thumb presented all thumb muscles, but these go to digit 2, which is now the most radial digit (Fig. 1). As also anticipated, in the hand with partial thumb duplication there is no duplication of the thumb muscles, supporting the results of experimental studies on mouse models showing that limb skeletal and connective/muscle tissue patterning can be uncoupled (e.g., Li et al., 2010). That is, the number of thumb muscles was not changed, but their insertions were changed according to the adult topological position of each of the two thumbs: the muscles that normally go to the radial (e.g., abductor pollicis brevis) and ulnar (e.g., adductor pollicis) sides of the thumb now attach onto the radial side of the most radial thumb and ulnar side of the most ulnar thumb, respectively (for more details, see Diogo et al., 2015a). Also in line with our model, recent comparative studies in vertebrates indicate that the developmental factors for skeletal morphological identity reside less than previously thought in the embryonic cell lineages, and more in the topological position in the embryo, allowing the relative position of bony elements to be highly conserved in evolution (Hirasawa and Kuratani, 2015). A "nearest-neighbor" model for limb muscle–bone, as well as for muscle–nerve connections, was proposed in the 1980s by Hinchliffe and Johnson (1980: p. 96–97), who stated that

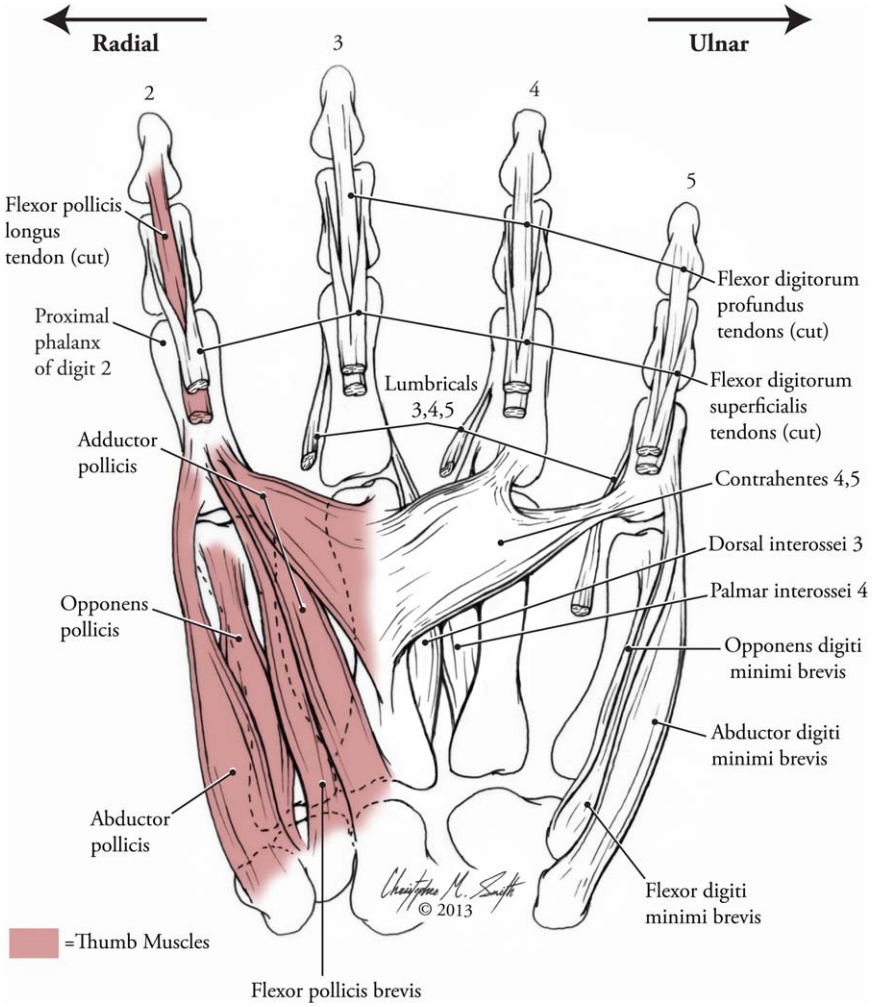

Fig. 1. Four-digit hand of a trisomy 18 human newborn, showing that the muscles that usually attach to the thumb in karyotypically modern humans now attach to the digit that as a homeotic identity of digit 2 and develops from the anlage of digit 2, but that is now the most radial digit due to the loss of the thumb. Illustration by Christopher Smith, modified from Smith et al. (2015a).

such a dynamic, flexible model ensures correspondence between these tissues during dramatic evolutionary changes and even in congenital malformations. Our "nearest-neighbor" model has also some similarities with Wolpert's "positional information" model, in the sense that the positional value of a cell/structure (e.g., in this case, the skeleton) can be recognized by—and affect the normal patterning/morphogenesis of—another cell/structure (e.g., in this case, tendons/muscles) without leading to a change in the overall phenotype/shape of that other cell/structure (Wolpert, 1969, 2011). In fact, according to Wolpert's model, muscle cells of limbs do not have positional values (contrary to limb skeletal tissues), so it would be reasonable to assume that they are affected by/follow the positional values of the skeleton, as proposed in our limb "nearest neighbor" model.

Recent studies have supported the idea that limb morphogenesis and adult structure and function are determined by close physical interactions between the limb's muscles, tendons, and skeleton (e.g., Blitz et al., 2013). For instance, Botelho et al.'s (2015) developmental work suggests that the delayed skeletal maturation/differentiation of metatarsal 1 seen in of most birds, associated with the early onset of activity of the muscles associated with this bone, probably lead to the characteristic "muscular twisting" of the avian opposable hallux. In addition, Huang et al. (2015) experiments in mouse embryos strongly suggest that autopod (hand/foot) tendons are dependent on—and probably induced by—cartilage formation, while zeugopod (forearm/leg) tendons are dependent on the presence of muscles. They proposed a model of limb development that is highly modular, flexible, and evolvable: the early formation of the cartilage-dependent autopod tendons is mainly decoupled from that of the muscle-dependent zeugopod tendons, with these two type of tendons only becoming associated at the level of the wrist later in development. That is, according to this model each extrinsic muscle of the hand and foot are formed by at least three modules with different developmental origins: the autopod tendon, the zeugopod tendon, and the muscle belly itself. The results of Huang et al. (2015) fit well with the "nearest neighbor" model because this model requires that the formation of autopod tendons is coupled with that of the autopod cartilages. As explained above, this coupling is mainly topological (physical), rather than related to the specific identity of the tendons and cartilages (see also Abdala et al., 2015), leading to a scenario that is even more flexible, and evolvable, than that proposed by Huang et al. (2015). That is, loss of a digit (e.g., digit 5) does lead to the loss of autopod tendons/muscles in the sense that there are no autopod tendons/muscles going

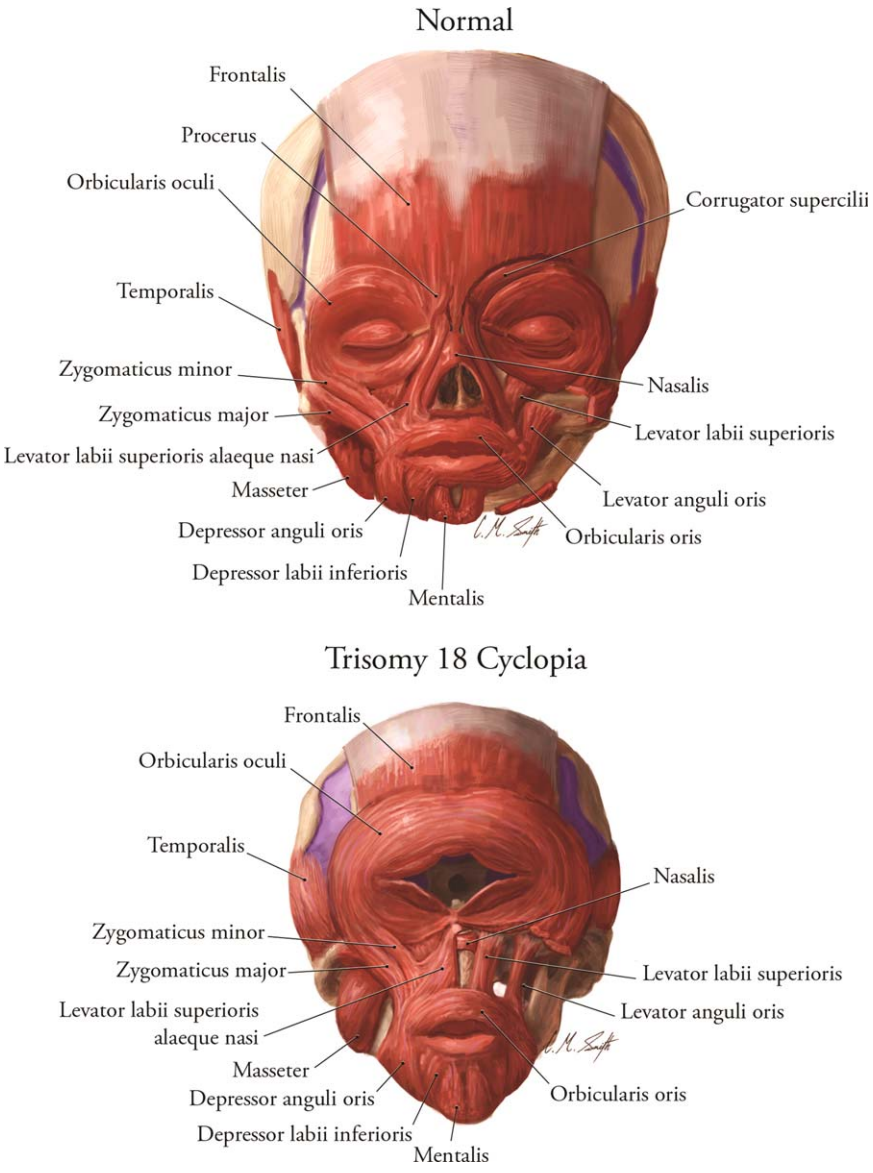

Fig. 2. Comparison of anterior head musculature usually present in karyotypically normal infants and in a trisomy 18 cyclopic fetus. The platysma myoides, risorius, and buccal fat pad were removed; left side shows deep dissection. Illustration by Christopher Smith, modified from Smith et al. (2015a).

nowhere in the adult autopod. But in nonpentadactyl animals that lack digit 5, the tendons/muscles that normally go that digit in other tetrapods tend to be present and attach to digit 4 instead, as described above for the salamanders. Therefore, the muscles that are missing—due to the coupling between cartilage and tendon formation described by Huang et al (2015)—are those that normally go to the middle digits (e.g., 2, 3, or 4), resulting in an overall configuration in which the number and configuration of the muscles that normally go to the more extreme digits (1 and 5) are usually kept. The "nearest neighbor" model also fits well with studies of Ros and colleagues, which have shown the occurrence of a cascade of tissue interactions during digit morphogenesis that induces first the skeleton, then tendons, and then the sculpturing of muscle bellies (Hurle et al., 1990; Ros et al., 1991). Recently, they have shown that the progressive reduction in *Hoxa13* and *Hoxd11–Hoxd13* genes from a *Gli3*-null background results in progressively more severe polydactyly in mice, displaying thinner and densely packed digits; combined with computer modeling, their results argued for a Turing-type mechanism underlying digit patterning, in which the dose of distal *Hox* genes modulates the digit period or wavelength (Sheth et al., 2012). If confirmed, such a mechanism would help to better understand limb malformations and explain some of the musculoskeletal patterns described in the paragraph above, in the sense that digits could be seen as belonging to three main types based primarily on their topological/physical position, as predicted by the "nearest neighbor" model: (a) most radial/tibial; (b) most ulnar/fibular; (c) all digits in between, which could have - in at least some cases - no specific, well-defined identity. These hypotheses need to be tested using a combination of developmental, experimental, pathological, and mathematical research, and that is precisely one of the main aims of our current work.

Such a "nearest neighbor" model of limb muscle-skeleton connections is markedly different from models normally proposed for the head and neck bones/cartilages and muscles derived from the

branchial arches (i.e., mandibular muscles, 1st arch; hyoid muscles, 2nd arch; branchial muscles, more posterior arches). Studies using rhombomeric quail-to-chick grafts to investigate the influence of hindbrain segmentation on craniofacial patterning showed that each rhombomeric neural crest cell population remains coherent throughout ontogeny, with rhombomere-specific matching of muscle connective tissue and their attachment sites for most branchiomeric muscles (e.g., Köntges and Lumsden, 1996). Köntges and Lumsden model is more a "*find and seek*" model because the muscle–bone associations are thus mainly related to the homeotic (arch) identity, rather than to topological position: muscles of an arch need to find and attach to skeletal structures through connective tissues derived from that arch. There are, however, a few known exceptions to Köntges and Lumsden's "*find and seek*" model, within the branchiomeric muscles. For instance, McClearn and Noden (1988) documented a few examples, in birds, of secondary movements in which muscle attachments changed considerably, and were unrelated to the myoblast-crest relations established earlier. Of interest, most mammalian facial expression muscles, which are derived from the second (hyoid) arch, attach onto structures that are *not* derived from this arch, including the skin, midfacial and jaw territories populated only by frontonasal and first arch crest cells, and even postcranial bones (e.g., clavicle: Noden and Francis-West, 2006; Diogo and Wood, 2012a). Also, Prunotto et al. (2004) showed that in terms of C-met mutations the facial muscles behave as limb and hypobranchial migratory muscles (i.e., tongue and infrahyoid muscles, which are somitic, and thus not branchiomeric, or true head, muscles) that normally migrate far away from their primary origin and that are absent in organisms with C-met mutations, contrary to other branchiomeric muscles.

Our recent studies of humans with birth defects also support the idea that facial muscles behave more like limb muscles than like other branchiomeric muscles, in the sense that they seemingly display a "*nearest neighbor*"—not a "*find and seek*"—model of muscle–bone association. First, as in the normal human population, in cases of human birth defects the facial muscles almost never attach to second arch skeletal structures. Second, in cases of severe skeletal malformations, the muscles react as predicted by the "*nearest neighbor*" model. For instance, in a trisomy 18 cylopic fetus missing a proboscis (and any structure that might correspond to an external nose) the nasalis muscle that normally goes to the nose still attaches to a supero-medial anteriorly directed prominence of the maxilla that lies in the region where the nose is usually located (Fig. 2). We have compiled 83 and 5 cases, respectively, of human limb and facial muscle congenital malformations (Smith et al., 2015a) in which it was possible to quantify the occurrence of a "*nearest neighbor*" pattern: 71% (59) of the limb and 80% (4) of the facial muscle cases did conform to this model. An illustrative example provided by other authors regarding the facial muscles concerned a case of mandibulofacial dysostosis in which, in the absence of the zygoma, the zygomaticus major/minor attached to the "nearest neighbor" (zygomatic process of the frontal bone: Herring et al., 1979). However, more cases need to be compiled, particularly for facial muscle defects, as the sample available is still very low.

Based on anatomical and developmental data obtained by us and others on humans, mammals, and other chordates (see Diogo and Ziermann, 2015) we can speculate that the "*nearest neighbor*" model of muscle-hard tissue associations is seemingly plesiomorphic for chordates, because it seems to be found often in nonchordate animals, including flies (Li et al., 2010; Schweitzer et al., 2010; Elly Ordan, personal communication). Then, due to the very complex shape and mainly spherical organization of the vertebrate head in which several structures are deeply interconnected a "*find and seek*" model of muscle-skeleton attachment for the branchiomeric muscles was acquired, using neural crests to ensure that these muscles attach onto structures derived from their respective arches, thus increasing the robustness of the whole head. This mainly spherical organization contrasts with the somehow more two-dimensional, rectangular (mainly proximodistally elongated) organization of the limbs, in which the musculoskeletal structures of different anatomical subregions are much less connected to each other, in the overall (see results of and discussion about our anatomical network analyses of heads vs. limbs in Smith et al., 2015a). This hypothesis makes sense because the presence of neural crest cells is a derived feature within chordates (for a recent review, see, e.g., Diogo et al., 2015b). The facial expression muscles are derived 2nd arch (hyoid) muscles only present in mammals and their reversion to the plesiomorphic "*nearest neighbor*" model would have allowed these muscles to break the relatively rigid constraints of the "find and seek" model. This idea is supported not only because the facial expression muscles share similar anatomical, developmental, and molecular features with the limb muscles as noted above, but also because the attachments, overall configuration and number of these muscles are particularly variable in mammals, including primates (Diogo et al., 2009b; Diogo and Wood, 2012a). In fact, these muscles are not only associated with the remarkably diverse facial expressions of mammals and particularly humans, but also with completely different functions, such as suckling or mastication in most mammals (e.g., buccinator muscle) and flying in mammals such as bats (e.g., occipito-pollicalis muscle: Tokita et al., 2012). This variation in muscle attachments is a prime example of phenotypic plasticity where genetic information cannot be used alone to predict morphology in an organism; the variable topological directed mode of attachment that may be driving limb and facial expression muscles probably cannot be detected merely through genetic means (West-Eberhard, 2003).

Developmental constraints, the notion of "phylotypic stage," internalism vs. externalism, and the "logic of monsters" vs. "homeostasis" views about human birth defects

The above examples and the generally predictable muscle changes associated with changes in the number/topological position of digits in both normal and abnormal individuals of different tetrapod taxa support Alberch's (1989) ill-named "*logic of monsters*" (LoMo). According to this theory, which was also based on a detailed skeletal study of digit reduction in amphibians (Alberch and Gale, 1985), there is a parallel between the variation/defects in normal/abnormal individuals of a certain taxon (e.g., modern humans) and the fixed diversity observed in wild-type individuals of other taxa (e.g., species of lizards or amphibians). Such a parallel was noted at the beginning of the 19th century by Meckel (1804), who based his studies on normal and abnormal development in humans and other animals stated that "the constant involvement of certain organs together in congenital malformations allows the conclusion that their development is coordinated under normal conditions" (cited in Opitz and

Reynolds, 1985). This parallel is achieved through regulation of a conserved developmental program (e.g., a set of genetic and/or epigenetic interactions) such that the structure of these internal interactions constrains the realm of possible variation upon which selection can operate (Alberch, 1989). In principle, such a program can break down in the evolution of some clades, but within most clades this would lead to death of the embryos (Alberch, 1989). A parallel between the more common phenotypic variations seen in the normal human population and malformations seen in birth defects is also to be expected according to the "*lack of homeostasis*" model by Shapiro et al. (1983). This model was in large part formulated based on observations of human trisomic individuals and states that, in such individuals, the presence of a whole extra functioning chromosome or of large chromosome segment causes a general disruption of evolved genetic balance. Because of the obligatory integration of the entire genotype this disruption affects the products of the trisomic chromosome and other chromosomes. This results in decreased physiological and developmental buffering against genetic and environmental forces. This in turn leads to a generalized decreased developmental and physiological homeostasis where the pathways and processes that will be the most often and seriously affected are those that are more unstable (leading to variations) in the normal population. An illustrative example, predicted by both the LoMo and "lack of homeostasis," is that a very common human variation (polymorphism)—absence of palmaris longus muscle, seen in circa 15–20% of normal population—is often seen, but amplified, in humans with severe congenital malformations—muscle absent in 74% (105) of 141 defective upper limbs we have reviewed in Smith et al. (2015a).

However, with exception to this similarity, the LoMo and "lack of homeostasis" models have very different assumptions and predictions. The latter model argues that defects are in general more *random* and disorganized due to a general lack of homeostasis (e.g., very often leading to left–right asymmetry), while the LoMo predicts that defects are more "logical" and "constrained" because constraints are in general still kept intact by internal homeostasis. Therefore, contrary to the "lack of homeostasis model," the LoMo predicts that congenital malformations and plastic variations found in a certain taxon often mirror features that are consistently found in individuals of other taxa. This prediction has been supported by studies showing that the existence of similar patterns of intra-specific diversity in a taxon (plasticity) and inter-specific diversity in different taxa is usually the result of similar developmental mechanisms (Hodin, 2000). The LoMo is thus framed in an "internalist" view of evolution and development that contrasts with the more "externalist" view of adaptationists, defending that selection by the external environment is the main evolutionary force. For instance, frogs and salamanders tend to lose/reduce digit 1 and digit 5, respectively, due to developmental constraints (the first digit to be lost/reduced is the last to form in development); the pattern remains even in frogs living in very different environments and exposed to markedly different external factors (Alberch and Gale, 1985).

One of the earlier more prominent defenders of internalism was Goethe. He profoundly influenced the Romantic German school (e.g., Oken) and *Naturphilosophie* (e.g., von Baer) and also Haeckel, at the end of the 19th century, as well as non-German researchers such as Owen (Richards, 2002) and Bateson (1894). Bateson compiled an impressive number of studies about animal morphology, human development, variations, and defects and defended ideas that are now becoming mainstream in Evo-Devo. For instance, he argued that variation is mainly due to internal mechanical (e.g., number of parts) or chemical (e.g., reactions leading to a certain color) factors (constraints) and that natural selection merely selects between a very limited/constrained number of phenotypes. In his outstanding book, Levinton (2001) expressed a similar view and defined developmental (internal) constraints as nonrandom (often noncontinuous) canalization of evolutionary direction due to limitations imposed by complex interactions of gene expression and epigenetic interactions in the developing organism. He argued that the use of, e.g., Turing-like mechanisms during development often leads to the formation of a discrete number of complete structures; so, in a way, ontogeny and thus evolution can be related to minor saltatory changes. He provided several animal case studies supporting a more internalist view of evolution and/or the LoMo but stressed that development is still probably more variable than defended by Pere Alberch. Arthur (1997) reported additional examples of variable development, even within a same genus, but noted that most of these examples referred to nonvertebrate, and particularly nonamniote organisms. He wondered why, considering overall life cycles, are von Baer's (voBa) laws (see Section 4) more pronounced in vertebrates than elsewhere? He answered that the high degree of embryo protection typical of vertebrates such as amniotes and particularly of placentals such as humans, probably considerably reduces the strength of external selection pressures in early development. Although positive internal selection may be involved in the origin of phylum-level body plans, subsequent internal selection would thus likely be negative, taking the form of a "developmental constraint." The importance of internal constraints has been recently supported by the use of a new tool—anatomical networks—for comparative, developmental, and evolutionary biology. For instance, the reduction of several skull bones (Williston's law) is a macroevolutionary trend (found across the ecologically diverse tetrapod clade) that can be explained by internal bias favoring the loss of the least connected bones (Esteve-Altava et al., 2013). We have recently expanded anatomical network analyses to include also muscle–muscle and muscle–bone connections, and to study human pathology as well (Esteve-Altava et al., 2015a,b; Smith et al., 2015a). Other recent studies on modularity, for instance about the modular heterochrony of dermal vs. endochondral bones, have also provided examples of internal constraints that might have been particularly important in vertebrate macroevolution (Koyabu et al., 2014).

This notion of internal constraints could help explain the results of our previous studies on the mode and tempo of primate and human evolution, particularly regarding the several examples where rates of muscle evolution in several lineages of each major primate clade are strikingly similar (Diogo et al., 2013d). According to the neutral model of evolution, this would be the expectation for molecular evolutionary changes. However, this had not been previously reported for any type of anatomical evolutionary changes, at least within the order Primates. In this sense, these results lend support to an internalist view of primate evolution because, for instance, despite the major environmental and climate changes in Africa in the last 25 Ma, the rate of muscle changes accumulated during that period at the nodes that lead to the Cercopithecidae and subsequently to the genus *Colobus*, and also to the *Cercopithecus* genus, is exactly the same (Diogo et al., 2013d). Moreover, these similarities in global rates

do not necessarily correspond to similarities in the rates for each different anatomical region: e.g., at the node leading to the Cercopithecidae, the rate for the head/neck changes is 0.19; at the node that leads to *Cercopithecus*, it is 0.38; and at the node that leads to *Colobus*, is 0.00; the respective rates for the forelimb are 0.19, 0.00, and 0.38.

From the point of view of "internalist" authors, the examination of these partial rates could be viewed as support for the idea that ontogenetic constraints are so interconnected and strong that the potential for global change accumulated in the different body regions is limited. This fits with the results of studies showing that in early development, principally during the "phylotypic stage," there is extensive interactivity among different modules of the body and, therefore, low effective modularity (e.g., Galis and Metz, 2007). Furthermore, it has been argued that from a developmental viewpoint, if substantial somatic investment is made in one structure of a module of the body, this could limit investment devoted to the formation of another structure from that—or another—body module (e.g., Galis and Metz, 2007). For instance, removal of the hindwing primordium in one side of the body of caterpillars results in an increase of weight of the adult butterfly forewing, thorax, and foreleg lying on that side, while the weight of these three latter structures does not change on the side where the hindwing primordium is intact (Hodin, 2000). It is possible that constructional trade-offs constrain investment in whole phenotypes because the structural space in organisms is limiting (e.g., Hulsey and Hollingsworth, 2011). Our examples of very stable muscle evolutionary rates *within* certain primate clades and of substantial rate differences *between* these clades support Pere Alberch's idea that punctuated equilibrium might be related to events of long-term (constrained) stability punctuated by periods of change (instability) due to the breaking of constraints (Diogo et al., 2013d). This idea is somewhat similar with modern ideas relating minor vs. major evolutionary transitions to changes in downstream genes (leading to specific/generic differences) vs. more internal portions (differences at the family, order, or class levels) vs. extremely conserved parts (differences at the phylum level) of genetic regulatory networks (Davidson, 2006). It is also somewhat related to De Beer's (1940) suggestion that more stable evolution related to anagenesis (phyletic change) and to peramorphic events (terminal additions/developmental acceleration) would be punctuated by major changes in evolution and evolutionary rates related to cladogenesis (branching) and to neoteny (juvenilization; form of paedomorphosis). This is because, in paedomorphosis, the deletion of terminal developmental stages would often lead to more generalized forms that may subsequently evolve in completely new ways; in contrast, in peramorphosis, addition of terminal stages would often result in very specialized forms adapted to very specific environments and, therefore, displaying relatively limited taxonomical diversity and low macroevolutionary potential (for more details, see Diogo and Ziermann, 2015). The definitions given in De Beer's (1940) *Embryos and Ancestors* were adapted and changed by Gould (1977), who stated that developmental retardation leads to *paedomorphis* (*neoteny*; somatic retardation) and recapitulation (*hypermorphosis*; retardation of maturation), as does developmental acceleration (recapitulation by means of somatic acceleration; paedomorphis by means of *progenesis*, i.e., acceleration of maturation). It should be noted that throughout the remainder of this study when we refer to retardation and acceleration of development we refer to somatic ontogeny, i.e., acceleration leading to *peramorphosis* and specifically to recapitulation, and retardation leading to paedomorphosis and specifically to neoteny (*Bolk's fetalization*; see below).

As noted above, some authors argue that the evidence for a "phylotypic stage" and for a voBa internalist evolutionary model is still scarce for nonvertebrate organisms (e.g., Bininda-Emonds et al., 2003) but probably applies better to amniotes and thus to mammals and primates (e.g., Arthur, 1997; Levinton, 2001). Galis (1999) reported that changes in the stable number of seven cervical vertebrae seen in almost all mammals are nearly always associated with neural problems and an increased susceptibility to early childhood cancer and stillbirths in humans. This is probably caused by breaking of developmental constraints: changes in the mechanisms (e.g., in *Hox* gene expression) leading to this number very likely perturb sensitive early stages of development such as the "phylotypic stage," leading to major abnormalities. Some recent studies argued to have provided evidence for a "molecular phylotypic stage" by showing a remarkably similar pattern of gene expression in early development of embryos from very diverse vertebrate clades (Elinson and Kezmoh, 2010). Other "molecular hourglass" models have been recently proposed for plants (Quint et al., 2012), flies (Ninova et al., 2014), and amniotes (Irie and Kuratani, 2011). The existence of a phylotypic stage (or a hourglass model of development), either molecular or phenotypic, is a major problem for voBa's law of divergence because divergence would apply only after this stage; in earlier stages development would be substantially variable and then mainly convergent (Arthur, 2002, Hazkani-Covo et al., 2005).

Our Evo-Devo-P'Anth studies and comparisons support the idea that internal constraints play a central role in not only normal, but also abnormal, human development, and thus Alberch's LoMo, because there are consistent patterns seen in both individuals with very different genetic syndromes and in variations of the normal human population. For instance, Wood (1867a,b, 1868) reported that muscle variations are much more frequent in the upper than in the lower limbs of the normal human population (292 vs. 119 cases in his sample, i.e., 71% vs. 29%). In our sample of 234 cases of muscle defects compiled from studies including both upper and lower limbs of humans with severe congenital malformations, the proportion was respectively 165 (34, 2, 22, 42, 37, and 28 for pectoral, dorsal and ventral arm, dorsal and ventral forearm, and hand) vs. 69 (4, 5, 2, 26, 12, and 20 for pelvic, dorsal and ventral thigh, dorsal and ventral leg, and foot muscles), so exactly also 71% vs. 29% (Smith et al., 2015a). Moreover, as explained in Section 1, within these limb birth defects there was a consistent pattern concerning muscle–skeleton attachments. Of interest, most of the defects found in the upper (65%) and particularly lower (84%) limbs are seen in the autopods and zeugopods, which are mainly evolutionary innovations of tetrapods; moreover, these more recent distal limb elements are positionally specified by members (i.e., 9 to 13) of the *Hox* gene family that are seemingly unique to vertebrates (e.g., Seth et al., 2012). This makes sense in an internalist view of evolution because these phylogenetically more recent innovations are also the last limb regions to form in development and, therefore, the ones more prone to developmental changes, variations, and defects (terminal changes; see below). It also makes sense in a more externalist view of evolution, as the more distal limb regions are in closer contact with prey/substrate/objects, so more prone to evolutionary adaptive changes. This link between the order in which morphological structures appear in evolution (phylogeny), development (ontogeny), interactions with the environment (ecomorphology), and thus evolvability

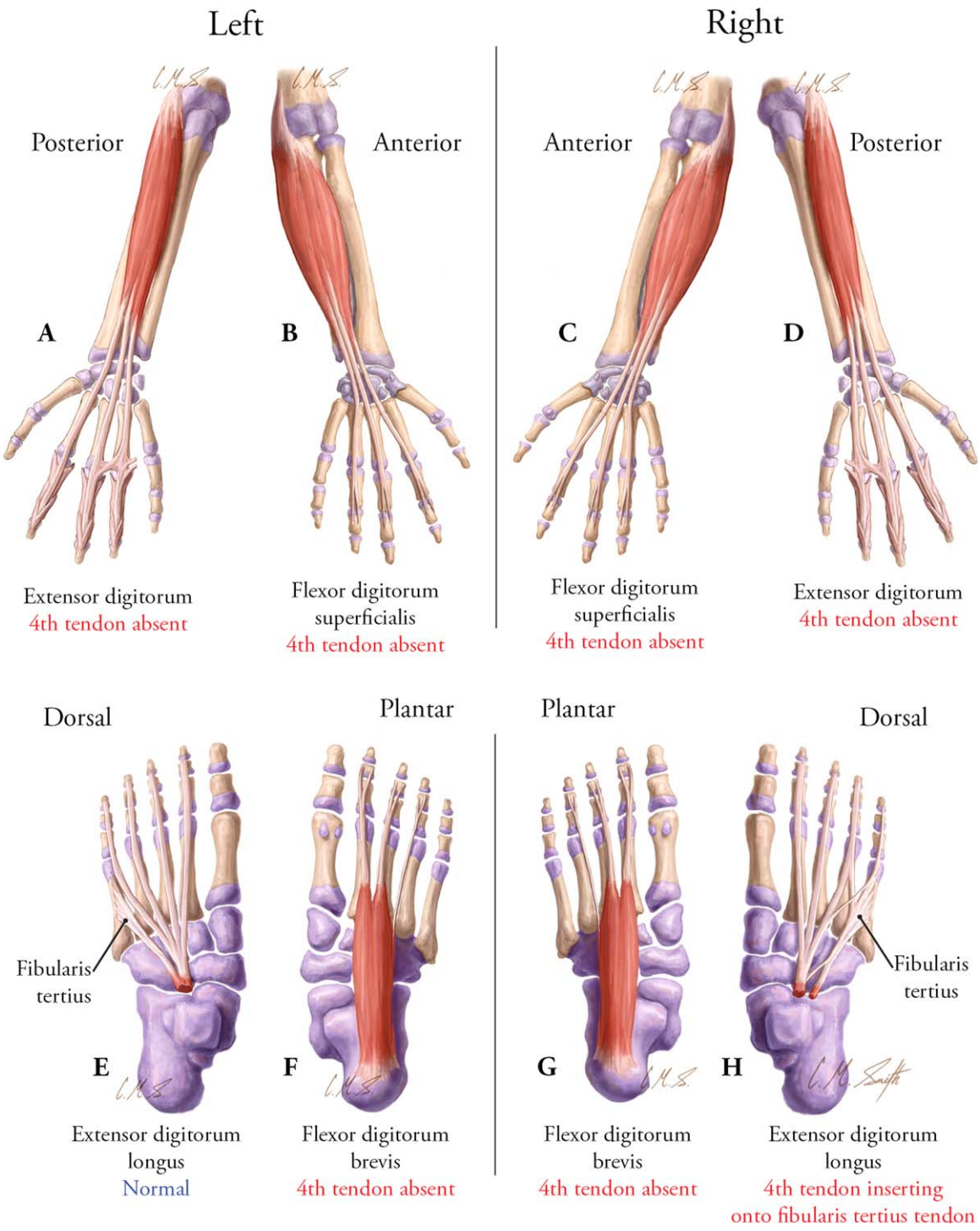

Fig. 3. Same trisomy 18 cyclopic fetus as in Figure 2, showing upper and lower limbs. Red indicates the tendon absent in all four limbs: 4th tendon to the 5th digit (**A–D,F,G**). Normal anatomy was observed on the dorsal surface of the left foot (**E**). The 4th tendon inserts onto a separate fibularis tertius on the dorsal surface of the right foot (**H**). Illustration by Christopher Smith, modified from Smith et al. (2015a).

(adaptation) supports the LoMo in the sense that it predicts a parallel between the normal and variant phenotypes of normal populations and defects in abnormal individuals. Of interest, within the 64 limb muscle defects we have compiled involving changes of attachment (origin/insertion), the changes of insertion tended to be toward more proximal limb regions (35, vs. 14 to more distal regions), while the changes of origin tended to be toward more distal regions (11 vs. 4 to more proximal regions) (Smith et al., 2015b). In total, most (49, or 76%) of the attachment changes concerned insertion changes (vs. 15, or 24%, origin changes). This is another parallel with phylogeny, because in primate/human evolution the majority of changes were also changes of the insertion sites of limbs muscles (61%, vs. 39% of changes of origin). This also makes sense within both externalism (as by definition insertions are more distal so concern regions that

are in more close contact with the outside) and internalism (e.g., ontogenetically the origin sites of limb muscles tends to form first, so terminal changes would affect more their insertion sites: Diogo and Tanaka, 2014; Diogo and Ziermann, 2014).

The upper limbs seem particularly prone to phenotypic changes and defects: within 316 defects compiled in studies including both head and upper and lower limbs, the proportion of upper limb defects (158, or 50%) is also substantially higher than that of head defects (94, or 30%) (64, or, 20%, being lower limb defects) (Smith et al., 2015a). Within the 94 head defects, there are 33, 29, 25, and 7 mandibular (1st arch), hyoid (2nd arch), branchial (posterior arches), and hypobranchial (somitic, tongue and infrahyoid) muscle defects, respectively. These numbers also support a "logical" link between evolution, ecomorphology, development, and birth defects. For instance, the vast majority (19 vs. 10, or 66% vs. 34%) of the 29 hyoid muscle defects concern the muscles of facial expression, which are topologically more superficial and are in fact more evolvable than other hyoid muscles. Contrary to other hyoid muscles, they also display a peculiar pattern of developmental migration (see above), and their overall shape only becomes similar to that seen in adults later in development than does the overall shape of other head muscles such as most branchial muscles and extra-ocular muscles. Similarly, the vast majority (19 vs. 7, or 76% vs. 24%) of the 26 branchial muscle defects concern the trapezius/sternocleidomastoideus complex (or protractor pectoralis in fish/amphibians), which is also topologically more superficial in adults, and more evolvable (Diogo and Wood, 2012a), than other branchial muscles and usually develops later than most other branchial muscles in normal development (e.g., in frogs, urodeles, and mammals: see, e.g., Edgeworth, 1935; Ziermann and Diogo, 2013, 2014). Another significant point supporting the LoMo is that, within the total 1,540 human muscle defects we have compiled, 1,044 (68%) are found in the left (522) and right (522) sides of a same individual, while only 496 (32%) are found in a single side (Smith et al., 2015a). The fact that a left–right symmetry is usually kept in individuals with severe congenital malformations, not only in nondefective structures but even in structures that are extremely defective themselves, does not support the "lack of homeostasis" model, which predicts a more random, and thus asymmetrical, distribution of defects (see above).

An illustrative case study supporting the LoMo concerns the limbs of the trisomy 18 cyclopic fetus shown in Figure 3. Despite the several malformations displayed by this fetus, there is an overall coherent, "logical" and predictable pattern in all four limbs. In both upper limbs the extensor digitorum tendon to digit 5 (i.e., 4th tendon) is missing; moreover, the tendon to digit 5 of the extensor digitorum longus (which topologically corresponds to the extensor digitorum in the lower limb) is also missing on the right foot. Furthermore, in both upper limbs the flexor digitorum superficialis is missing the tendon to digit 5, and in both lower limbs the flexor digitorum brevis (which topologically corresponds to the extensor digitorum in the lower limb) is also missing a tendon to this digit. In addition, the tendons to digit 5 of all these muscles are often missing in both variations of the normal human population and in the normal phenotype of various nonhuman taxa (Diogo and Wood, 2012a), as predicted by the LoMo (see also Section 3). Importantly, all these similarities between the defects of the dorsal and ventral muscle masses of the upper and ventral limbs are seen only in the zeugopods and autopods, supporting the idea that these similarities are due to a very strong developmental link resulting from a derived, homoplasic co-option of similar genes to form these muscle masses on the distal—and evolutionarily new/derived—portion of the four limbs (Diogo et al., 2013c; Diogo and Tanaka, 2014). In fact, the dorsoventral symmetry and upper–lower limb similarity are seemingly even more constrained than the left–right symmetry in some cases. For example, in the same trisomy 18 cyclopic fetus the right leg and forearm short extensors that normally go to digit 2 (extensor digitorum brevis bundle going to digit 2 and extensor indicis, respectively) go instead to digits 2 and 3, while on the left side they have a normal insertion to digit 2 only (Smith et al., 2015a). In striking contrast, within the numerous defects found in this fetus, there is not even a single similarity between defects of muscles attached to the phylogenetically older pectoral vs. pelvic girdles.

Human evolution, reversions, atavisms, paedomorphosis and peramorphosis

Diogo and Wood (2012b) stressed that reversions played a substantial role in primate/human evolution because 1/7 of the 220 (i.e., 28) evolutionary changes unambiguously optimized in the most accepted primate phylogenetic tree are reversions to a plesiomorphic state. Of those 28 reversions, 6 are directly related to our own evolution because they occurred at nodes that lead to the origin of modern humans, and 9 go against Dollo's law (which states that once a lost complex structure is unlikely to be regained). Our Evo-Devo-P'Anth studies support the idea that reacquisition in adults of morphological structures that were missing in adults for long periods of time is possible because the associated developmental pathways were kept in the members of that taxon. For instance, chimpanzees display a reversion of a synapomorphy of the Hominidae (great apes and modern humans; acquired at least 15.4 Ma ago) in which adult individuals have two contrahentes digitorum other than the muscle adductor pollicis, which is the only contrahens muscle present adults of other hominid taxa: one going to digit 4 and the other to digit 5. Developmental studies of hand muscles (e.g., Cihak, 1972) showed that karyotypically normal human embryos *have* contrahentes going to various fingers; however, these muscles usually are reabsorbed or fuse with other structures during later embryonic development. Furthermore, in karyotypically abnormal humans, such as those with trisomies 13, 18, or 21, the contrahentes often persist—as "atavisms"—until well after birth (e.g., Dunlap et al., 1986). Atavisms are coordinated, often incomplete structures that appear as developmental anomalies and resemble ancestral character states of the taxon to which the individual belongs (Levinton, 2001). Cihak (1972) showed that intermetacarpales are also present as discrete muscles in early embryonic stages of karyotypically normal modern humans, before they fuse with some flexor breves profundi muscles to form the muscles interossei dorsales. Therefore, the evolutionary reversions resulting in the presence of contrahentes and discrete intermetacarpales in extant chimpanzees are likely related to heterochronic—and specifically paedomorphic—events in the lineage leading to chimpanzees (Diogo and Wood, 2012b). That is, in this respect extant chimpanzees are seemingly more neotenic than humans (see below).

According to some authors, cases where complex structures are formed early in ontogeny just to become lost/indistinct in later developmental stages (the so called "hidden variation") may allow organisms to have a great ontogenetic potential early in

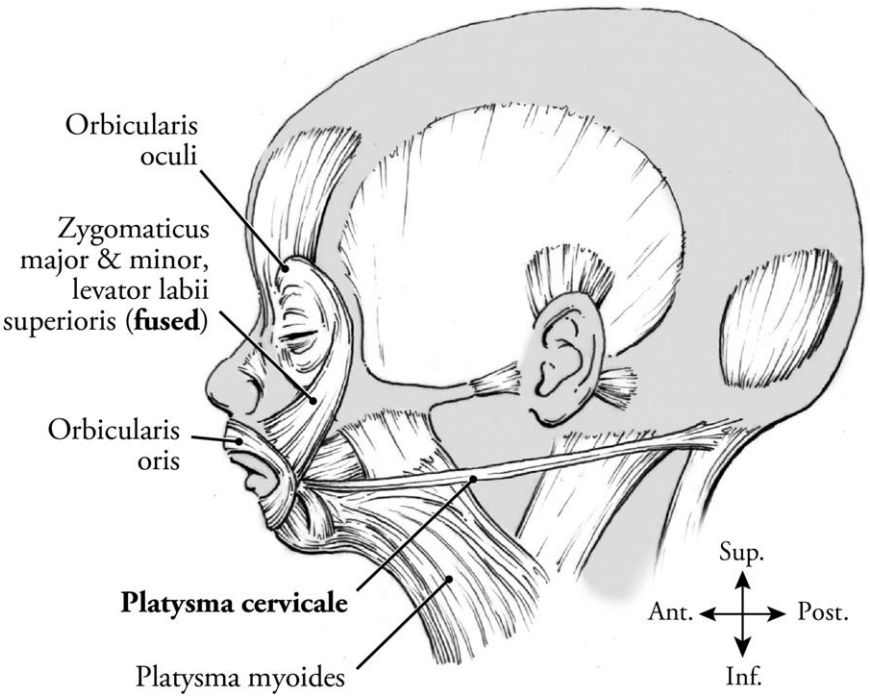

Fig. 4. Baby with Down syndrome showing platysma cervicale originating with the trapezius from the occipital bone and inserting onto the corner of the mouth; the zygomaticus major and minor and the levator labii superioris are fused, forming a thin sheet originating at the corner of the orbicularis oculi. Anomalies labeled in bold. Illustration by Julia Molnar, modified from Bersu (1980).

development, so that if faced with external perturbations (e.g., climate change, habitat occupied by new species) evolution can use that potential (adaptive plasticity: e.g., West-Eberhard, 2003). However, as explained above, authors such as Gould (1977, 2002) and Alberch (1989) suggested that the occurrence of such cases support a "constrained" (internalist) rather than an "adaptationist" (externalist) view of evolution. In fact, it is intuitively unlikely that the persistence of contrahentes (and of the platysma cervicale: see Fig. 4 and below) in the later developmental stages of karyotypically abnormal humans (e.g., with trisomies 21, and particularly 13 and 18, which usually die before or soon after birth: Section 4), is due to natural selection and adaptive evolution. This fits with the idea defended by Galis and Metz (2007: 415–416): "without denying the evolutionary importance of phenotypic plasticity and genetic assimilation, we think that for the generation of macroevolutionary novelties the evidence for the impact of hidden variation is limited" (see also Levinton, 2001). As noted above, we tend to subscribe to the view that hidden variation may have a limited role in the generation of evolutionary novelties, but it may have a more important role in the *reappearance* of some traits associated with these novelties, as in anatomical reversions that violate Dollo's law. Importantly, the platysma cervicale, contrahentes digitorum, and intermetacarpales of karyotypically "normal" human embryos do not correspond to the muscles of *adult* primates such as chimpanzees or of other adult mammals; instead, they correspond to the muscles of the *embryos* of the latter taxa (Diogo and Wood, 2012a,b). The developmental pathways resulting in the presence of these muscles in adults of these latter taxa were not completely lost in modern humans, even after several million years, likely because these pathways are associated (pleiotropy) to those recruited in the formation of other structures that *are* present and functional in modern human adults.

Examples of abnormal human "atavisms" that were historically used to support Haeckel's recapitulation (HaRe) theory- and thus the importance of peramorphosis in human evolution (e.g., Wiedersheim, 1895; Davidson, 1914) - were summarized and criticized by De Beer (1940) and more recently by Verhulst (2003). For instance, Darwin and many other 19th century authors considered as an "atavism" the presence, in some human newborns, of a tail-like appendage at the height of the coccyx or lumbar spine. Verhulst attacks that idea by pointing out that these appendages are very different from animal tails, e.g., they almost never contain bones (vertebrae) or cartilage. However, it should be noted that some authors have described muscles associated with these tail-like structures that, according to them, do resemble caudal muscles of other animals (Wiedersheim, 1895). It is also clear that many of the so-called "atavisms" described in trisomic humans by authors in the, 1970s, 80s, and 90s (e.g., Barash et al., 1970; Dunlap et al., 1986) cannot be atavisms by definition, because those features were never present in our direct ancestors (Diogo and Wood, 2012a,b, 2013 Smith et al., 2015a). However, some muscles variants of the normal human population or in humans with congenital malformations are in fact atavistic (e.g., opponens hallucis, dorsoepitrochlearis, epitrochleoanconeus, levator claviculae), although it is not clear if their presence is due to a developmental delay or not. More detailed studies on the ontogeny of these structures in humans and other animals, and particularly primates, are needed to clarify these issues.

Hall (1984) reviewed some examples of potential atavistic features in humans and other animals and suggested that the presence of such features as human variants might represent maintenance of a polymorphism in the normal human population. For instance, the muscle palmaris longus is present in circa

80–85% of the normal human population. As in most primate taxa this muscle is present in approximately 100% of the normal population, there is supposedly a trend toward a decreased frequency of this muscle in human evolutionary history (Diogo and Wood, 2012a,b). If this is so, it is likely that in the future this muscle may be present in just a very small percentage of the normal adult human population, and can thus be seen as a rare, "atavistic" variation/anomaly. That is why, although atavistic features are often related to developmental arrest/delay/retardation and thus to the process that leads to paedomorphosis, they are often used by authors defending the importance of the opposite phenomenon, i.e., of peramorphosis/recapitulation. These authors use cases of *abnormal* development in which paedomorphosis leads to atavisms to support their theory that the opposite occurred in human evolution, i.e., that those atavistic structures were once normally seen in adults but then, due to peramorphosis, became only present in earlier stages (as, e.g., the platysma cervicale) of, or even completely absent in, ontogeny. The followers of Bolk's (1926) fetalization theory (i.e., that humans are instead mainly neotenic apes), which was partially accepted by Gould (1977), want instead to find cases of paedomorphosis in *normal* human development to support the idea that this phenomenon was important for the evolution of normal human anatomy. The example of the palmaris longus also stresses an important point made by Holmes (1944): that, *although it is not common, it is likely that there are some examples of HaRe in the literal sense*. That is, as the late fetal and adult configuration of the human palmaris longus are essentially the same (Bardeen, 1906), if in the future this muscle will be present until late fetal stages and then be always missing in adult stages of the normal human population, the fetal stage will in fact be similar to the adult ancestral stage.

What can be said with more confidence is that many of the examples provided by Verhulst (2003) to support Bolk's fetalization theory are clearly as flawed as many of the erroneous "atavistic" examples provided in the past to support the opposite (recapitulation) theory. For example, in a desperate attempt to fit the very complex and derived human hand in Bolk's fetalization theory, he argues that the configuration of the human hand actually represents the ancestral, fetal stage, and that gorillas subsequently lost (in evolution/development) the ability to use the precision grip. Apart from embryological and morphological studies (e.g., Diogo et al., 2012b), recent genetic studies supported the highly derived character of the human hand. For instance, Prabhakar et al. (2008) suggested that there was a gain of function in one of the most rapidly evolving human noncoding elements (*HACNS1*) in the human hand, which likely altered the expression of nearby genes during limb development (N.B. some aspects of that study are still controversial: Terence Capellini, personal communication). However, it should be emphasized that humans do seem to have neotenic features. For example, it is accepted that the skull of apes and humans closely resemble one another early in development, and that subsequently the facial region develops more slowly in humans, retaining the proportion of juvenile apes (Carroll, 1997). Some detailed comparisons regarding other features, such as the neuronal system, have also supported the idea that human brain development is retarded when compared with that of other primates, particularly in some association areas related to episodic memory, social navigation, and planning, allowing us to retain juvenile characteristics/learning over a long-lifetime (neoteny: Bufill et al., 2011). This neotenic ability to retain such juvenile features over a long-lifetime due to a retarded development seems to be combined with an accelerated prenatal development of the brain in humans (Sakai et al., 2012), emphasizing the point the a same taxon can display a mosaic of retardation/acceleration features, even within the same organ/anatomical region. One interesting pattern regarding the vast majority of these and other examples provided in the literature about differences between the ontogeny of humans and other primates, either to support neotenic or peramorphic views of human evolution, is that they almost all refer to examples of *terminal* addition/acceleration (leading to peramorphosis) or deletion/retardation (leading to paedomorphosis). That is, these examples seem to support Levinton's (2001) view that changes in development are mostly terminal. This also makes sense according to the idea that earlier developmental stages in vertebrates are particularly sensitive and/or prone to internal constraints (e.g., phylotypic stage, see Holland, 2014, and above).

Curiously, some examples are used by various authors to support HaRe and by other authors to support the opposite idea, i.e., Bolk's human fetalization. For instance, the supposed resemblance of some so-called "hairy humans" to other primates has been interpreted by some as an atavism that would support Haeckel's view of evolution. However, as stressed by Leroi (2003, p. 285), "both the hairy Burmese and Canary Islanders are described as having exceptionally fine, silken hair; this does not really resemble the robust pelt that covers adult apes" but instead the "fine, silky" "lanugo" hair of human fetuses. This abnormality is thus probably due to a developmental arrest/delay, and emphasizes again the major error of Haeckel's theory: the hair of human fetuses does not resemble the hair of adult apes, being instead probably more similar to the hair of ape fetuses. In fact, hair itself was also used as an example of human neoteny (paedomorphosis) to support Bolk's "fetalization theory." This is because ape newborn gorillas have hair on the head and short, "lanugo"-like hair in the rest of the body; their characteristic hairy coat does not appear until later stages (Held, 2009). In this case, human adults would be seen as neotenic. However, with respect to hair humans are both neotenic and peramorphic in the sense that they not only not form a hairy coat (terminal deletion of ancestral character) but actually also loose even the "lanugo" body hair during normal development (terminal addition of special, derived character). That is, this is a further example of a parallel between development (humans loose "lanugo" body hair during development) and evolution (human adults lost most body hair during evolution), but not of human neoteny (paedomorphis) or recapitulation (paedomorphis).

In summary, what seems clear is that humans have a mosaic of both paedomorphic and peramorphic features, and that only a more detailed, careful, systematic, and less tendentious study comparing normal and abnormal human development with the development/adult anatomy of other animals can help quantifying the specific contribution of each of these two events during human evolution. What can be said is that, within the 1,540 cases of human muscle congenital malformations we have compiled (Smith et al., 2015a), 257 (17%) are potential atavisms and 352 (23%) can potentially be due to developmental delay. Therefore, if more detailed comparative developmental studies confirm that these numbers, or even just a substantial portion of them, are truly atavistic and/or due to developmental delay, these would be significant proportions. Of interest, within these 1,540 cases, 650 (42%) concern the presence of abnormal structures (e.g., muscle heads/slips or tendons); 590 (38%) concern the complete absence, while

only 145 (9%) and 66 (4%) concern respectively fusions and complete duplications, of muscles usually present in the normal human population. Within the defects occurring in pentadactyl limbs, there were 9, 30, 18, 8, 22 abnormal muscle structures going to hand digits 1, 2, 3, 4, and 5, respectively, and 4, 2, 0, 1, 1 going to foot digits 1, 2, 3, 4, and 5, respectively. Number of absent muscle structures was 60, 18, 2, 2, and 39 for structures associated to hand digits 1, 2, 3, 4, and 5, and 2, 0, 1, 1, 32 for structures associated with foot digits 1, 2, 3, 4, and 5. Therefore, with the upper plus lower limbs there was a total of 13, 32, 18, 9, and 23 abnormal structures going to digits 1, 2, 3, 4, and 5, while there was a total of 62, 18, 3, 3, and 71 absent structures going to these digits. These numbers make sense within the LoMo, because usually in mammalian development digits 1 and 5 are among the last to form (4→3→5→2→1 for some authors, but recent studies in mice indicate that it might be 4→3→2→5→1: e.g., Raspopovic et al., 2014; Bardeen's, 1910, detailed study of human development also suggested that digits 1 and 5 are usually the last to form in both our hand and foot). That is, it is expected that cases of absence (e.g., due to developmental delay) will mostly affect muscles going to these digits, and less so muscles going to digits 4 and 3, which are the first to form. Before ending this Section, it is important to stress that, despite the potentially substantial proportions of atavisms and/or developmental delays mentioned above, these phenomena still are a minority within all cases of birth defects we have compiled. This supports the results of other anatomical studies of trisomic human individuals suggesting that apart from developmental retardation, many other factors are probably involved with the defects found in these individuals, including the aberrant organization of primordia (e.g., presence of two, rather than three, pulmonic valve cups) and misdirected morphogenetic movements (e.g., leading to abnormal innervation of muscles or "horseshoe kidney": e.g., Barash et al., 1970).

Scala naturae, Haeckel's recapitulation, von Baer's laws, and the parallelism between phylogeny and development

The examples, given in Section 3, of evolutionary reversions, particularly in human evolution, go against the notion of progress and purpose of evolution, which is in turn closely related to the rise of developmental theories such as HaRe (e.g., Gould, 1977). This theory was based on a "*scala naturae*" view of nature in which white human males were seen as more complex and, therefore, placed at the top of the scale. This scheme had profound and extremely unfortunate social and racial implications and, unfortunately, continues to be deeply embedded in some current textbooks and scientific papers (Diogo et al., 2015c). Regarding HaRe, this theory is no longer accepted because, as noted above and as stated in voBa's 4th law, the ontogeny of an animal does not, in general, recapitulate the *adult* stages of its ancestors; NB: voBa's three other laws are: (1) general features of the embryo appear earlier than special features; (2) special characters develop from general characters through the increase of tissue and organ differentiation; (3) embryos of different species progressively diverge from one another during ontogeny (Abzhanov, 2013). However, researchers often use this theory as a "straw-man" to deny that there is often a parallel between phylogeny and development. According to Gould (1977), such a parallel exists and it is probably driven more by phylogenetic/ontogenetic constraints than by adaptive plasticity. This view was also supported by Levinton (2001), based on his compilation of a large amount of data from both extant and fossil animals. He did list examples provided by De Beer (1940) to contradict HaRe: "teeth evolved before tongues, yet tongues appear before teeth in mammalian development," but then stated that a review of the data available suggests that ontogeny and phylogeny are in fact often intimately related because evolution usually involves terminal additions (Levinton, 2001: p. 219–220; but see Mabee, 1993). Levinton argued that HaRe can in fact be considered a special case of voBa's law in which evolutionary terminal additions play a central role, and formulated his own, more specific ontogenetic–phylogenetic laws: (1) many major structures have some form of integration through development; (2) the development of the structure involves an order of appearance of substructures (e.g., proximodistal elaboration of the tetrapod limb); (3) when an order exists, evolutionary modifications tend to favor developmentally later stages first; (4) developmentally later stages, in general, probably are of lower burden and are most subject to change.

Our Evo-Devo-P'Anth studies do show that, in the case of the muscles of zebrafish, salamanders, and frogs, the order in which muscles appear in ontogeny is usually similar to the order in which they appeared in phylogeny (Diogo et al., 2008b; Ziermann and Diogo, 2013, 2014; Diogo and Ziermann, 2014; Diogo and Tanaka, 2014; Diogo et al., 2015a-c, in press). The parallelism between phylogeny and development is also supported by studies on human evolution and ontogeny. For instance, the flexores breves profundi normally appear in 13.5 mm (total length) human embryos; the intermecarpales, lumbricales, contrahentes, and dorsometacarpales at 14 mm; the abductor pollicis brevis at 15 mm; and the abductor digiti minimi at 16 mm (Cihak, 1972). All these structures were acquired phylogenetically before the origin of mammals (Diogo and Tanaka, 2012). The adductor pollicis, opponens digiti minimi, and flexor digiti minimi brevis appear in human ontogeny before, 20 mm; these structures are found in mammals such as monotremes and rats. The opponens pollicis and flexor pollicis brevis appear at 28 mm; these muscles are only consistently found in primates. Then, the contrahentes become completely undistinguishable at 35 mm; these muscles were phylogenetically lost in the node leading to hominids (i.e., great apes and humans).

Importantly, the re-absorption or fusion of structures such as the contrahentes, as well as the intermetacarpales or platysma cervicale of the "lanugo" hair (Section 3), during normal human development does not match the expectation of voBa's second law. According to this law, a more general "mammalian" configuration (e.g., having body hair, or contrahentes) should be followed by an *increasing tissue and organ differentiation, i.e., the development of specialized, more derived structures from the general* (Abzhanov, 2013). voBa stressed that there is no "trend toward perfection" during human development, as defended by some supporters of HaRe, but did state that there is a "trend toward complexity" in development (Gould, 1977: p. 55). However, the examples provided show that, in reality, there are many cases in which there is instead a *simplification/loss* of structures during human ontogeny. Similar examples concern human embryonic development, where morphogenesis of five pairs of aortic arches (which once sent blood to the gills) is followed by a complete destruction of two of them. As put by Held (2009: 67), this "only makes sense as a historical constraint: it must have been (. . .) easier to reconfigure the existing plumbing than to scrap it altogether and start afresh." This also occurs during the development of

many other chordate taxa studied by us. For example, in neotenic salamander species such as axolotls that lack a full metamorphosis, some muscles become indistinct/lost/reabsorbed during ontogeny (e.g., the pseudotemporalis profundus and levator hyoideus become integrated in the pseudotemporalis superficialis and the depressor mandibulae, respectively; Ziermann and Diogo, 2013). Another example concerns the notochord, which is present in adult stages of phylogenetically basal chordates and remains present in early development of vertebrates. This is probably due to the fact that the physical presence as well as the signals emanating from the notochord are essential prerequisites for differentiation and morphogenesis of the spinal cord, vertebrae, and gut tube structures (see, e.g., Holmes, 1944; Gilbert, 2010). Evolutionary tinkering, in other words (Jacob, 1977). Of course, there are also examples of muscle differentiation in human ontogeny, e.g., the rhomboideus becomes divided into a rhomboideus major and minor, and the extensor carpi radialis divides into brevis and longus (Bardeen, 1906; Lewis, 1910). Importantly, these examples that conform more to voBa's second law also support a parallelism between phylogeny and development because adult tetrapods first had undifferentiated rhomboideus and extensor carpi radialis muscles; each of these muscles then became subdivided later in tetrapod evolution (Diogo and Wood, 2012a).

Another major problem of voBa's theory, which had been stressed by some in the past but unfortunately continues to be largely neglected nowadays, is *the lack of a dynamic, evolutionary perspective* (Slaby, 1990). voBa was an antievolutionist; his best works were done in the 1820s before the publication of Darwin's books and were, therefore, mainly against "Romantic evolution," but toward the end of his life he did publicly opposed Darwin. Therefore, voBa's rules presuppose rigidity and immovability over time, while in reality the "general" and the "specific" in evolutionary morphogenesis are continuously in motion: the general changes to the specific and the specific to the general and both categories undergo incessant changes (Slaby, 1990). For instance, birds never develop teeth during normal development: the general tetrapod (or gnathostome) configuration—having teeth—is no longer found at all, while some specific features appear immediately on the threshold of morphogenesis. Avian neural crest cells are competent to induce teeth but the avian oral epithelium has lost the ability to respond properly, even though the coding region for enamel is still present in modern birds (Kollar and Fisher, 1980; for a more recent work on the subject and a description of generic correlates, see Meredith et al., 2014). As a result, the embryos of birds and other reptiles do not "keep up" with each other during the earlier stages of development, and a feature that was surely present in the avian ancestors is completely missing in normal bird ontogeny. Therefore, this example contradicts even a "von Baerian" type of recapitulation, i.e., where the embryo of the offspring should be identical or resemble the embryo of the ancestors, and not the adult animal as stated in HaRe (Løvtrup, 1978; Slaby, 1990). That is why De Beer (1940) proposed the term "repetition" (ontogeny repeats phylogeny) and Holmes (1944) speaks more of "parallelism."

In this study, we formally define this phenomenon as "*Phylo-Devo parallelism*," to avoid confusion with "evolutionary parallelism," which refers to the resemblance between the evolutionary history of two different taxa, and not between evolution and development. *Phylo-Devo parallelism* thus refers to the fact that *in most cases of phenotypic change occurring in the normal development of a certain taxon, the order of the developmental changes is similar to the order of evolutionary (phylogenetic) changes that occurred during the evolutionary history of that taxon.* This is different from HaRe because there is no necessary reference to adult forms, i.e., the parallelism applies both to adult (in the few cases where there is a literal HaRe: see above) and nonadult stages. It is also different from von Baerian recapitulation (sensu Løvtrup, 1978) because not all stages seen in the embryos of the ancestors are necessarily "recapitulated" (e.g., teeth are never seen in bird development). It is also different from voBa's laws because it provides the dynamic evolutionary frame stressed by Slaby (1990) and thus removes the rigidity/immovability about the general, the specific, and the supposed trend toward increasing tissue and organ differentiation from the general condition to the specialized, more derived structures. It can thus account for atavisms, which are complex structures that were once general but are now almost completely suppressed from development: e.g., in normal human development the platysma cervicale (see Fig. 4) is formed and then become absent during development (Gasser, 1967), mirroring its appearance in the mammalian clade and disappearance in our more recent evolutionary history.

We should, however, emphasize the fact that although the *Phylo-Devo parallelism* is apparently the rule—at least within the musculoskeletal system of the numerous vertebrate taxa for which we have compiled data so far—there are some exceptions, so it is *not* an absolute law. For instance, within the 58 head muscles of zebrafish, salamanders, and turtles for which we explicitly compared "phylo vs. devo" data, only five (8.6%) break this rule (2 of 29, 2 of 23, and 1 of 6 in zebrafish, axolotl, and *Trachemys*, respectively: Diogo et al., 2010; Diogo and Abdala, 2010; Ziermann and Diogo, 2013). Contrary to the cases conforming to the *Phylo-Devo parallelism* rule, which are very likely due to internal constraints as explained above, the exceptions to this rule probably include a substantial proportion of cases related to direct adaptations to external conditions. For instance, one of the five exceptions concerns the fact that in 4-day zebrafish larvae the levator arcus branchialis 5 is already much more developed than other branchial muscles, before the adductor mandibulae splits into bundles, while in evolution the hypertrophy of the former muscle occurred in the node leading to the Cypriniformes, much later than the division of the adductor mandibulae into bundles (Diogo et al., 2008b). The alteration of the levator arcus branchialis 5 and of the skeletal element that is moved by it—the ceratobranchial 5—is related with the specialized feeding mechanisms of Cypriniformes, in which ceratobranchial 5 bears teeth and ossifies earlier than other ceratobranchials—a case of developmental acceleration. Such coordinated developmental timing changes may, therefore, ensure proper size relationships between myological and skeletal structures (Diogo et al., 2008b). This supports the idea that cases of Phylo-Devo parallelism are probably related to the idea that most major phenotypic changes occur later in development due to internal constraints, while exceptions to this rule are related to earlier changes that are likely related to the breaking of those constraints and that, if viable, have a high adaptive/cladogenetic potential. In this case, the peculiar acceleration of development of the levator arcus branchialis 5 and ceratobranchial 5 in cypriniforms is related to a peculiar synapormorphy of these fishes—the acquisition of a new, pharyngeal jaw—that very likely contributed to their huge taxonomical diversity (e.g., Diogo, 2007). Another type of cases in which exceptions to the *Phylo-Devo parallelism* are expected are those in which markedly different developmental processes lead to similar adult configurations, e.g., due to canalization (i.e.,

buffering of a phenotypic character against variation in the ontogenetic mechanisms that construct it: Rice, 1998). In some such cases, the developmental differences can be attributed to selection acting directly on early ontogenetic stages associated, for instance, to life-history changes such as a shift from indirect to direct development. We recently provided examples of some changes in the order of muscle appearance in the heads of frogs with direct vs. indirect development, which have a very similar adult configuration (Ziermann and Diogo, 2014). However, there are also major changes in early developmental stages that do not appear to be under direct selection and continue to produce a similar adult morphology (Rice, 1998). As explained above, the order of formation of the hand digits in salamanders is the opposite to that seen in frogs (radio-ulnar vs. ulno-radial) due to internal constraints. However, due to other types of internal constraints (e.g., leading to a consistent pattern of topological muscle–bone spatial associations: Section 1), the overall adult muscle configuration of the hands of frogs is generally similar to that seen in salamanders (Diogo and Tanaka, 2014; Diogo and Ziermann, 2014). For a few other examples of exceptions to *Phylo-Devo parallelism*, see, e.g., Weisbecker et al. (2008), Koyabu and Son (2014), and Smith (2006).

The fact that most authors, including voBa, tend to neglect the common occurrence of secondary loss/simplification of structures during development is very likely due to a strategy that is often followed in developmental biology: *idealization* (Love, 2010). That is, developmental biologists tend to see phenotypic variation and secondary loss/simplification during the development of wild-type model organisms, and also humans, as noise. Examples of this are the very simplified—and erroneous—descriptions of muscle development in humans as a trend of progressive structural differentiations (Diogo et al., in press). Another example is the establishment of "normal stages" of development of model organisms under strict laboratory conditions to intentionally minimize developmental plasticity and thus to have "standardized" comparisons of their "normal" phenotype in different laboratories around the globe (Love, 2010). As a self-criticism, we can thus admit that, although we try to take into account the occurrence of variations in both normal and abnormal development, particularly in humans as stressed above, our more internalist view of evolution and development may be partially influenced by the fact that most data available on model organisms was obtained under such "idealized" conditions. That is, these data very likely do not reflect the true developmental plasticity of organisms, and thus the importance that external conditions might potentially have in generating this plasticity (see West-Eberhard, 2003). We plan to specifically study and quantify the variation of soft tissues during the development of various model organisms in a future work.

Patau, Edwards, and Down Syndromes (trisomies 13, 18, 21); atavisms; apoptosis; and heart malformations: medical implications and the future of Evo-Devo and Evo-Devo-P'Anth

To investigate the developmental mechanisms related to the atypical development and abnormal phenotype of striated muscles in human trisomic individuals and compare them with the processes leading to phenotypic variation in humans, we are studying cadaveric material from fetal, neonatal, and adult humans with trisomies and from mouse models for Down syndrome (DS) (e.g., Ts65Dn). Skeletal studies of trisomic human individuals have supported the idea that, in at least some aspects, there is in fact a developmental delay, e.g., in trisomy 21 some nasal bones develop after the 24th week, while in karyotypically normal humans, the age of developmental onset is the 10th week (e.g., Keeling et al., 1997). Of interest, these skeletal studies provided examples of different phenotypic patterns often seen in different trisomies, for instance regarding the axial skeleton in trisomy 18 vs. trisomy 21 fetuses (Keeling et al., 1997), further supporting the LoMo. The main hypothesis we now want to test is that the disappearance of muscles such as the contrahentes and platysma cervicale (Fig. 4) during early developmental stages of karyotypically normal humans is related to apoptosis, and thus that the frequent persistence of these atavistic muscles until later ontogenetic stages in individuals with trisomies 13 and 18 and 21 is associated with a delayed development specifically due to a decreased muscle apoptosis. It has been suggested that humans with DS show an increase of apoptosis in neurons, granulocytes, and lymphocytes (e.g., Elsayed and Elsayed, 2009). If our studies support the hypothesis that these individuals have decreased muscle apoptosis, to the point of often having additional muscles in later ontogenetic stages, this would suggest a more nuanced story with respect to apoptosis (i.e., a mosaic scenario where there is more apoptosis in some tissues and less in others). In fact, within the numerous DS cases listed in the tables of Dunlap et al. (1986), there are 12 supernumerary muscles vs. 2 absences (and various variations) in total, so there are more additional muscles in general, supporting our hypothesis that individuals with DS might have decreased apoptosis in skeletal muscles. Bersu (1980) also suggested that the abnormal persistence of some embryonic muscles in later stages of development of trisomic individuals probably has to do with failure of normal cell death or some other process of involution. Moreover, by implying there is possibly a mismatch between the nervous (e.g., more apoptosis of cells of neurons) and muscular (i.e., less apoptosis and presence of extra muscles) systems, our hypothesis might also shed light on the etiology of hypotonia (low muscle tone) that is present in almost all babies with DS.

From a developmental genetic perspective, it is now known that members of a small family of proteins, termed MCIP1 and MCIP2 (myocyte-enriched calcineurin interacting protein), are most abundantly expressed in striated and cardiac muscles and that such proteins form a complex with calcineurin A; *DSCR1* encodes MCIP1 (e.g., Gotlieb, 2009). MCIP family expression is up-regulated during the differentiation of muscles; its forced overexpression inhibits calcineurin signaling, and this leads to a decrease of muscle apoptosis. Abnormal reduction of apoptosis in trisomic mice embryos can result in excess populations of myocytes being formed in the atrioventricular region, where they may interfere with the normal migration of cells during development of the heart. This leads to the occurrence of atrioventricular or ventricular septal defects and valvular abnormalities similar to the congenital heart defects typically seen in humans with DS (Gotlieb, 2009). Therefore, it is particularly interesting to note that one of the very few anatomical features that is regularly used today for prenatal screening of trisomies 13, 18 and 21 is the presence of "nuchal thickness." For instance, in DS 40–50% of affected fetuses have, in the late first-trimester, such a nuchal thickening ≥ 6 mm; nuchal translucency is a ultrasonographic method developed to measure fetal nuchal soft tissues at earlier stages (first trimester), which is now able to identity 83% of trisomy 21 pregnancies (Renna et al., 2013). Some authors relate

"nuchal thickness" to the presence of an abnormal soft tissue nuchal fold and/or altered composition of subcutaneous connective tissue, while others consider that it is the result of congenital heart disease and lymphatic obstruction (Spencer et al., 2000; Renna et al., 2013). Nuchal thickening might thus be related, either directly or indirectly, to low apoptotic levels of nuchal muscle (e.g., abnormal presence of a platysma cervicale: Fig. 4) or connective/other type of soft tissue or, more likely, of cardiac muscle (e.g., leading to heart defects). It may in fact be related to all these reasons: recent discoveries of a developmental cardiopharyngeal field have strongly linked the development of head, neck, and heart muscles and thus of the connective tissues associated to these muscles (Diogo et al., 2015b). Be that as it may, the fact that nuchal translucency is now a highly specific marker of not only trisomy 21 but also of trisomies 13 and 18 provides support to the LoMo in the sense that syndromes caused by trisomy of completely different chromosomes result in similar phenotypic features. Furthermore, this example also emphasizes, and clearly illustrates, how developmental and anatomical studies of trisomies and other birth defects and comparisons with normal development and anatomy can have crucial implications and applications for medicine.

The issues discussed in this study also have major implications for Evo-Devo and for Evolutionary Biology in general, because they are in line with recent works stressing that the study of natural variations and pathologies should play a more predominant role in these biological fields. Some of these works inclusively use the term "Evolutionary Teratology" or "Evolutionary Pathology" to refer to a new, and much needed, subfield of Evo-Devo (e.g., Guinard, 2014). The main difference between such a subfield and the one proposed in the present work is that the authors of those works use mainly other animals (e.g., dinosaurs) as their main teratological/pathological case studies, while in *Evo-Devo-P'Anth*, we use our own species and the data obtained from medical pathology and/or direct examination of both normal and abnormal humans and their development as the main, central case study. Guinard's (2014) recent study is particularly interesting because it shows how the relatively short forelimbs of dinosaurs such as the Tyrannosauridae display features that are strikingly similar to features associated with well-known human pathologies (e.g., micromelia). Therefore, by combining this information with data from developmental biology and human medicine concerning, for instance, developmental rates, *Hox* genes, growth factors and developmental pathways associated with these pathologies, one can try to better understand dinosaur evolution. More important for the purpose of this review, these examples further support the *LoMo* of Alberch by stressing that pathological features of one taxon (e.g., humans) are often seen as the normal phenotype of another taxon (e.g., dinosaurs), thus leading to a resurgence of the ideas defended by Isidore Geoffroy Saint-Hilaire, more than 150 years ago: "Monstruosity is no longer a blind disorder but another order, also regular and subject to laws" (Guinard, 2014: p. 21).

Similar ideas have also been defended recently by authors such as Palmer (2015), who pointed out a fact that is unfortunately not stressed as often as it should be and that has profound evolutionary implications: in general natural selection reduces variability because, as its name indicates, it *selects* one specific feature/some specific features among many available ones. For instance, positive selection of one of the many features present in organisms with a high developmental plasticity may lead to the genetic assimilation of that feature, and thus to the fixation of that feature in the normal phenotype during evolution (West-Eberhard, 2003). So, where does variability come from, in the first place? It may come from different processes, such as genetic mutations or events that are not directly related to mutations. According to Palmer (2015), the pronounced cases of left–right asymmetry seen in the crustaceans studied by him are probably not so much due to genetic/genomic changes, but rather to epigenetic events, which probably played a major role in the origin of anatomical innovations. This is because of all cases of asymmetry studied by him, none seems to be correlated to specific, heritable genetic changes—at least within those known so far; instead, there is evidence that in at least some crabs the choice of the side of the body that will have the larger claw is simply do to differential use (i.e., the first time that the crabs use the claws, they use that side). In fact, in taxa with such pronounced external asymmetrical features the asymmetry develops later in development, further supporting the idea that such features may be mainly due to epigenetic/functional factors and, again, that evolution often operates by means of terminal, or at least late, changes in development.

By putting together the data presented in those recent studies with the results obtained from our own works, there seems to be a very thin line between normal variations (which broadly correspond to normal developmental plasticity, or the "norm of reaction" of Evo-Devo) and malformations (which can be due either to genetic causes, the environment, and/or to other causes leading to developmental defects, and which correspond to the "teratologies" sensu Guinard, 2014). Development can be so complicated, and dependent of so many interacting factors, that it is subjected to numerous spontaneous errors (Guinard, 2014). As explained above, if for instance certain variations are positively selected (as facial asymmetry seems to be, in recent human evolution: e.g., Diogo et al. in press), or if some malformations are neutral and later—or from the beginning—positively selected or retained for any other reason, this can lead to cases in which such variations/malformations will be present in the normal phenotype later in evolution. This is what happened, very likely, during the evolution of the relatively short forelimbs of Tyrannosauridae and of the pronounced asymmetry seen in various crustacean taxa. Therefore, as stressed by Guinard (2014), the absolute negative side associated with developmental variations/anomalies, which is clearly seen in the use of the term mal("bad") -formation, and the "straw-man" misinterpretation of Goldshmidt's "hopeful monsters", should disappear from both evolutionary biology and Evo-Devo: "a prosperous teratology (anomaly) must instead be considered as a form of success, being an 'adaptation' or not" (Guinard, 2014: p. 36). In turn, the insights provided in the present study should guide human pathologists, medical researchers and students, as well as biological anthropologists in general to be more alert and pay more attention to human anatomical variations, and further study and discuss human anatomical defects. Therefore, we hope that the subjects discussed in the present study, and *Evo-Devo-P'Anth* in particular, will have an impact in evolutionary, developmental, and comparative biology and in various other biological fields, as well as in medicine.

Acknowledgments

Research by J.M.Z., C.S., and R.D. has been supported by a start-up package from the Howard University College of Medicine to R.D., and a PhD scholarship from the Howard University Graduate School to C.S. We thank two anonymous reviewers, as well as Tatjana Buklijas, for a detailed review of previous versions of this study and for their wise comments.

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