Dinosaurs, Chameleons, Humans, and Evo-Devo Path: Linking Étienne Geoffroy's Teratology, Waddington's Homeorhesis, Alberch's Logic of "Monsters," and Goldschmidt Hopeful "Monsters"

Article *in* Journal of Experimental Zoology Part B Molecular and Developmental Evolution · November 2016

DOI: 10.1002/jez.b.22709

CITATIONS
26

READS
1,144

3 authors:

Rui Diogo
Howard University
351 PUBLICATIONS **4,723** CITATIONS

SEE PROFILE

Geoffrey Guinard
8 PUBLICATIONS **95** CITATIONS

SEE PROFILE

Raul Epiblast Diaz
California State University, Los Angeles
30 PUBLICATIONS **672** CITATIONS

SEE PROFILE

REVIEW

Dinosaurs, Chameleons, Humans, and Evo-Devo Path: Linking Étienne Geoffroy's Teratology, Waddington's Homeorhesis, Alberch's Logic of "Monsters," and Goldschmidt Hopeful "Monsters"

RUI DIOGO[1]*, GEOFFREY GUINARD[2], AND RAUL E. DIAZ JR.[3,4]

[1]Department of Anatomy, College of Medicine, Howard University, Washington, District of Columbia
[2]UMR CNRS 5561, Biogéosciences, Université de Bourgogne, Dijon, France
[3]Department of Biology, La Sierra University, Riverside, California
[4]Natural History Museum of Los Angeles County, Los Angeles, California

ABSTRACT

Since the rise of evo-devo (evolutionary developmental biology) in the 1980s, few authors have attempted to combine the increasing knowledge obtained from the study of model organisms and human medicine with data from comparative anatomy and evolutionary biology in order to investigate the links between development, pathology, and macroevolution. Fortunately, this situation is slowly changing, with a renewed interest in evolutionary developmental pathology (evo-devo-path) in the past decades, as evidenced by the idea to publish this special, and very timely, issue on "Developmental Evolution in Biomedical Research." As all of us have recently been involved, independently, in works related in some way or another with evolution and developmental anomalies, we decided to join our different perspectives and backgrounds in the present contribution for this special issue. Specifically, we provide a brief historical account on the study of the links between evolution, development, and pathologies, followed by a review of the recent work done by each of us, and then by a general discussion on the broader developmental and macroevolutionary implications of our studies and works recently done by other authors. Our primary aims are to highlight the strength of studying developmental anomalies within an evolutionary framework to understand morphological diversity and disease by connecting the recent work done by us and others with the research done and broader ideas proposed by authors such as Étienne Geoffroy Saint-Hilaire, Waddington, Goldschmidt, Gould, and Per Alberch, among many others to pave the

*Correspondence to: Rui Diogo, Department of Anatomy, College of Medicine, Howard University, Washington, DC 20059.
E-mail: rui.diogo@howard.edu
Received 16 June 2016; Revised 29 September 2016; Accepted 3 October 2016
DOI: 10.1002/jez.b.22709
Published online in Wiley Online Library (wileyonlinelibrary.com).

J. Exp. Zool. (Mol. Dev. Evol.) 00B:1–23, 2016

way for further and much needed work regarding abnormal development and macroevolution. *J. Exp. Zool. (Mol. Dev. Evol.) 00B:1–23, 2016.* © 2016 Wiley Periodicals, Inc.

How to cite this article: Diogo R, Guinard G, Diaz Jr RE. 2016. Dinosaurs, chameleons, humans, and evo-devo path: Linking Étienne Geoffroy's teratology, Waddington's homeorhesis, Alberch's logic of "monsters," and Goldschmidt hopeful "monsters". J. Exp. Zool. (Mol. Dev. Evol.) 00B:1–24.

Congenital malformations (anomalies and birth defects) are structural or functional defects that lead to abnormal embryonic morphogenesis and/or metabolism and arise due to genetic, environmental, nutritional, or a combinatorial deficiency (Epstein et al., 2008). Globally, the prevalence of congenital malformations is 1 in 33 live births (~3%; Center for Disease Control and Prevention, 2016), with 276,000 not surviving past their first month of life (World Health Organization, 2015). Malformations present a major public health challenge as treatment throughout the lifetime of an individual, such as in cases of fetal alcohol syndrome, may cost up to $2 million while in total for the United States exceeds $4 billion annually (Lupton et al., 2004). More importantly is the human component itself: malformations usually have substantial aesthetic, functional and/or social detrimental effects not only for the individuals having them but also for their families and broader social networks.

Ranking behind heart defects, limb abnormalities have a prevalence of ~6/10,000 births (with upper extremities affected more than lower; Ermito et al., 2009) and craniofacial defects being present in approximately one-third of all neonates with congenital malformations (Hennekam et al., 2010). While the source for most abnormal phenotypes remains unknown, 30% of known cases are due to "simple" effects such as single gene Mendelian and non-Mendelian mutations, chromosomal defects, and teratogens, while the remaining 70% are due to more "complex" scenarios such as gene–gene and/or gene–environmental interactions (Hobbs et al., 2002). Perturbations of morphogenesis are primarily due to altered cell behaviors such as proliferation, contact, death, migration, and differentiation occurring abnormally, such as in defects of facial morphogenesis (Trainor, 2010). As cellular behavior is dependent on the genes that cells express (or suppress) as a result of extrinsic and intrinsic molecular cues activating gene regulatory networks, these upstream transcription factors are ultimately responsible for the development of the building blocks that make up organisms, such as organs, body parts, and cell types (Peter and Davidson, 2015).

Broad phylogenetic sampling of species supports the conclusion that the primary genetic circuitry involved in organismal development was present in the most recent common ancestor of bilaterian organisms approximately 600–800 million years ago (Knoll and Carroll, '99). Subsequent evolution of genomic architecture and cis-regulatory elements leading to invertebrate and vertebrate organisms with diverse body plans (Pires-daSilva and Sommer, 2003; Peter and Davidson, 2011). The conservation of signaling pathways and their associated hierarchy of proteins (i.e., transcription factors, structural proteins, and enzymes) has allowed for the use of organisms in the lab as models for understanding the biochemical and morphogenetic function of proteins affected by sequence mutations and environmental perturbations associated with human congenital phenotypes (Bier and McGinnis, 2003). Due to the high conservation of such developmental genes, it is expected that perturbation of the same genes in invertebrate and vertebrate model systems should lead to similar disruptions in embryonic morphogenesis (Reiter et al., 2001). With the sequencing of the human genome and widespread use of genome-wide association studies and next-generation sequencing (NGS) technologies to identify loci and genes associated with diseases, the utilization of model organisms to understand the function of identified candidate genes and mutations within a multicellular context is expected to rise.

Surprisingly, in the context of the emphasis of developmental biology ("devo") within evo-devo (evolutionary developmental biology) since the rise of this field in the 1980s, few authors have attempted to combine the knowledge obtained from the study of model organisms and from human medicine with data available on comparative anatomy and evolutionary biology to investigate the links between development, pathology, and macroevolution (Diogo, 2016). Fortunately, this scenario seems to be slowly changing, with a renewed interest in evolutionary developmental pathology (evo-devo-path) in the past few decades, as evidenced by Gunter Wagner's idea to publish this special, and very timely, issue on "Developmental Evolution in Biomedical Research." Because the three of us have recently been involved, independently, in works related in some way or another with evolution and developmental anomalies (Diaz and Trainor, 2015; Guinard, 2015, 2016; Diogo et al., 2015a; 2015b), we decided to combine our different perspectives and backgrounds in the present contribution for this special issue.

Therefore, in the section Brief Historical Introduction to Studies on Links between Evolution and Developmental Anomalies, we will provide a brief historical account on these issues. Then, in the sections Macroevolutionary and Paleontological Works as Case Studies, Developmental and Genetic Works as Case Studies, and Human Pathology and Development as Case Studies, we will do a review of the recent work done by each of

us, within different fields of science, that is, mainly regarding paleontology, evo-devo, and human evolution and pathology. Then, these four sections will be connected in the general discussion, provided in the section Intellectual Connections and Broader Evolutionary Implications, on the broader developmental and macroevolutionary implications of recent studies done by us and others, and how they connect with the broader ideas proposed by authors such as Étienne Geoffroy Saint-Hilaire, Waddington, Goldschmidt, Gould, and Per Alberch. In particular, our primary aims are to highlight the strength of studying developmental anomalies within an evolutionary framework to understand morphological diversity and disease by connecting, in that general discussion, the results of recent works with Waddington's notion of homeorhesis, Goldschmidt's hopeful "monsters", and Per Alberch's logic of "monsters," among many other previous ideas, in order to pave the way for further and much needed work regarding abnormal development and macroevolution.

BRIEF HISTORICAL INTRODUCTION TO STUDIES ON LINKS BETWEEN EVOLUTION AND DEVELOPMENTAL ANOMALIES

Of the three main components of evo-devo-path (Diogo et al., 2015b), pathology—and particularly human congenital malformations—has interested both erudite and lay people since thousands of years ago, including Aristotle (Leroi, 2014). A key person that influenced many authors that have attempted to discuss both the reasons behind and the broader implications of human congenital malformations after the so-called scientific revolution was Goethe (1749–1832). This is because Goethe was one of the earlier more prominent defenders of internalism, which had a great impact in the Romantic German school (e.g., Oken) and *Naturphilosophie* (e.g., von Baer), as well as on non-German researchers such as Owen and Bateson (Richards, 1992, Richards, '92, 2002, 2008).

According to Goethe, internal forces (e.g., developmental ones) are the main sources for the phenotype, while the environment mainly plays a secondary role in selection between the limited morphological diversity created by these internal forces (Richards, 2002). This idea is somewhat similar to that now defended by some proponents of the "extended evolutionary synthesis" (e.g., Pigliucci & Müller, 2010). In particular, Bateson (1894), influenced by Goethe's ideas, 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 constrained number of phenotypes.

Étienne Geoffroy Saint-Hilaire (1772–1844), who has been described as the "father of evo-devo" (Panchen, 2001), was also influenced by Goethe. Étienne's evolutionism "emerged from nature philosophy, which stressed 'unity of plan' ... he had realized that an accidental or environmentally imposed alteration in the development of an embryo would change the ultimate form of the mature organism; so, the earlier deviation of embryonic development, the more magnified the change would be in the adult" (Le Guyader, 2004). For Étienne, "monstrosity" was at a high, special level among anatomical anomalies, differentiating from all the dominant characters defining each species. His intention was to consider "monsters" without prejudices and study them through the identifiable and classifiable facts. Thus, it was necessary to also think beyond the deviation from the original shape (Ancet, 2006; see Geoffroy Saint-Hilaire, 1818–1822).

By means of Étienne's theory of the unity of organic composition or the continuity of organization between beings, "monstrosity" was discussed within an overall frame of the organization plan through rules, including the "principle of connections" or the "balancement of organs" (Ancet, 2006). That is, for him, order exists in the apparent disorder, which leads to establish a classification grouping individuals under the heading of common deformities. These links between development and deviation of form were experimentally studied by Étienne (Rostand, '64; Duhamel, '72) and further explored by his son, Isidore Geoffroy Saint-Hilaire (1805–1861), who introduced the term "teratology" as the science of anomalies within organismal organization (Geoffroy Saint-Hilaire 1832–1837). A current definition of teratology underlines a "discipline devoted to the study of congenital morphological anomalies, their causes and teratogenesis" (Dictionnaire médical de l'Académie de médecine, version 2016-1). The study of teratology has thus emerged within a comprehensive theoretical framework of the organization of life, with the ability of features to be passed from one species to another through transformation (Étienne Geoffroy St-Hilaire, 1825).

Already in the 20th century, Waddington ('42, '52a, '52b, '53a, '53b, '53c, '53d, '56, '57, '61a, '61b, '75) further discussed developmental perturbations and their effects on the phenotype and implications for "monstrosity." Specifically, he coined the term "canalization" for those features of developmental pathways that lead to the production of standard and discrete phenotypes despite environmental or genetic influences that would otherwise disrupt development (reviewed by, e.g., Hall, 2001, 2003). That is, canalization buffers physiological and metabolic systems against environmental and genetic perturbations, and by doing so allows genetic/developmental variability to build up within the genotype, even though such variability is not expressed phenotypically. A crucial point for the sections below is that, as noted by Balon (2004: 42–43), authors often refer to

Waddington's notions of homeostasis, canalization, and genetic assimilation, but not so much to his concept of homeorhesis. Balon stated: "in contrast to homeostasis as a process keeping something at a stable or stationary state, Waddington proposed for living systems the term homeorhesis, meaning stabilized flow ... the stabilization of a progressive system acts to ensure that the system goes on altering in the same sort of way that it has been altering in the past ... therefore we may define, for our purposes, any steady state as homeostasis and any stabilized state as homeorhesis." That is, homeorhesis can in theory lead to major, organized changes by stabilizing them.

According to Balon, "during a stabilized state ... the homeorhetic processes of the system 'resist' destabilization for as long as possible, enabling structures to be completed and functions to progress without interfering with stabilized life activities." However, when a system is destabilized, "a switch is rapidly made via a far from stable threshold into the next stabilized state of ontogeny ... the system will assume a new steady state upon the crossing of the threshold, and the resulting phenotypic transformations will then depend on the reaction norms of the system at this point, as well as on the secondary reactions of associated systems." The notion of homeorhesis thus may be useful to explain the occurrence of saltatory ontogeny and saltatory evolution *sensu* Balon, being somewhat related to the notion of "facilitated variation" *sensu* Gerhart and Kirschner (2005, 2007). These authors proposed (2007: 8582) that "the number and kinds of regulatory genetic changes needed for viable phenotypic variation are determined by the properties of the developmental and physiological processes in which core components serve, in particular by the processes' modularity, robustness, adaptability, capacity to engage in weak regulatory linkage, and exploratory behavior." Therefore, "these properties reduce the number of regulatory changes needed to generate viable selectable phenotypic variation, increase the variety of regulatory targets, reduce the lethality of genetic change, and increase the amount of genetic variation retained by a population; by such reductions and increases, the conserved core processes facilitate the generation of phenotypic variation, which selection thereafter converts to evolutionary and genetic change in the population."

Importantly, these ideas are also related to one of the most emblematic, and extreme, examples of an internalist view of evolution, Alberch's ('89) ill-named logic of "monsters." According to this theory, which was based on a detailed skeletal study of digit reduction in amphibians (Alberch and Gale, '83, '85), there is often a parallel between the variation/defects in normal/abnormal individuals of a certain taxon (e.g., modern humans) and the usual wild-type configuration seen in other taxa (e.g., species of lizards or amphibians). Such a parallel was also noted at the beginning of the 19th century by Meckel, who 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, '85). 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, '89). In principle, such internal constraints can break down in the evolution of some clades, but while in most clades this would lead to death of the embryos due to internal selection, members of other taxa might eventually survive until adulthood (see Diogo et al., 2015).

The internalist framework of the logic of "monsters" thus contrasts with the more externalist view of adaptationists, who defend that the current form of organisms is mainly explained by the external environment in which they live, and not by internal factors. For instance, frogs and salamanders tend to lose/reduce digit I and digit V, respectively: the first digit to be lost/reduced is the last to form in the development of each taxon. Such a pattern seems to be mainly due to developmental constraints, because, for instance, the reduction/loss of digit I is seen in frogs that live in very different environments and that are exposed to markedly different external factors (Alberch and Gale, '85). Similar examples concerning hand/foot skeletal elements, but of mammals, have been provided recently by Senter and Moch (2015). Another example provided by Alberch ('85) also concerns mammals, and specifically St. Bernards dogs, which usually have an extra (sixth) digit probably related to their larger size and larger limb buds—smaller dogs of other species almost never have an extra digit and often even lack some digits—and not because the presence of the sixth digit is adaptive per se.

More recently, Guinard (2015) proposed the concept of evolutionary teratology based on the notion that current and extinct wild types of certain taxa arose through deviations of "normal" development that could be seen as developmental anomalies. For him those deviations are not necessarily drastic; that is why he made a distinction between his conception and some of the notions related with Goldschmidt's hopeful "monsters." Goldschmidt ('40) introduced the concept of developmental macromutations—that is, mutations of important developmental genes that can produce significant phenotypic effects—to explain macroevolution. Although the vast majority of such mutations would be disastrous ("monsters"), there may be one macromutation leading to the adaptation of an organism to a new way of life—a hopeful "monster." Therefore, macroevolution would occur with the rare success of hopeful "monsters" rather than by an accumulation of small changes in populations. However, as explained by Guinard, this notion is often misinterpreted as the achievement of "perfection" in a jump (extreme saltationism), and Goldschmidt is often used as a "straw-man." The examples provided by Guinard, which will be described in section Macroevolutionary and Paleontological Works as Case Studies, emphasize that pathological features of one taxon (e.g., humans) are often seen as the normal phenotype of another taxon (e.g., di-

nosaurs), nevertheless support some of Goldschmidt's ideas and thus contributed to the resurgence of ideas defended by Étienne and Isidore Geoffroy Saint-Hilaire, more than 150 years ago: "monstrosity is no longer a blind disorder but another order, also regular and subject to laws" (Guinard, 2015: 21).

The renewed interest in Goldschmidt's ideas is particularly felt in evo-devo. For instance, Schlichting and Pigliucci ('98: 34) emphasize that Goldschmidt's view of macroevolution was much more complex and comprehensive than the caricature that neo-Darwinists have tried to create. Specifically, they state that Goldschmidt actually "pointed out plentiful experimental evidence for the dramatic phenotypic effects of macromutations, for example, the contrast of the normal diploid tobacco plant with several trisomic lines originates by chromosomal mutation; the range of morphologies and architectures was staggering, and all the plants were healthy and capable of surviving under natural conditions." In fact, one could also add that the criticism of Goldschmidt's hopeful "monsters" by neo-Darwinists was facilitated by a biased, anthropocentric view of evolution. This is because in humans any "macromutation" such as a chromosomal mutation tends to lead to the death of individuals, well before they reach sexual maturity and thus before being able to leave descendants, except in cases such as trisomy 21 (associated with Down syndrome). However, in many other animals, and particularly in other organisms such as plants, similar macromutations very often do not have the same dramatic effect as they have in humans, leading to healthy and viable organisms, as evidenced by the huge chromosomal diversity seen in not only different taxa, but also in cases within a same taxon (see, e.g., Levin, 2002). We will further discuss below the links between the topics addressed in this section, based on empirical data obtained in our own studies (sections Macroevolutionary and Paleontological Works as Case Studies, Developmental and Genetic Works as Case Studies, and Human Pathology and Development as Case Studies) and also from studies of other authors (section Intellectual Connections and Broader Evolutionary Implications).

MACROEVOLUTIONARY AND PALEONTOLOGICAL WORKS AS CASE STUDIES

The concept of evolutionary teratology *sensu* Guinard originated from the identification of complete and evolutionary cervical homeoses in penguins (Guinard and Marchand, 2010; Guinard, 2012). By extension, other types of developmental anomalies can be identified as evolutionary products. The limbs of tetrapods offer a promising field of investigation because of the variation in shape proportion and the number of elements and because of our strong modern foundation on the biology and developmental genetics of limb formation and growth.

In particular, evolutionary teratology encompasses developmental anomalies in general, minor or drastic, with organisms maintaining an overall viability with descendants—since the main focus is evolution. Why have developmental anomalies and teratology not been a more important part of evolutionary discussions? Mainly because the adaptationist framework followed by many neo-Darwinists limits this perception. For instance, the drastically modified forelimbs of a cetacean or a pterosaur are judged positively because they are supposedly "adapted" to the aquatic or aerial environment, respectively. Nevertheless, sticking such labels on these limbs does not say anything on their substance and, accordingly, when an anatomical structure does not meet such a requirement it is considered as "bizarre" and misunderstood because it cannot be seen positively within such an adaptationist paradigm. Determining an "adaptation" for everything is forgetting that organisms exist through each of their parts. It is the global functional outcome, interacting with the circumstances, which matters to draw a conclusion on the viability and thus the sustainability: this is the principle of the vital balance *sensu* Guinard (2015, 2016). With evolutionary teratology, the anomaly is identified in the first place, by incorporating an evolutionary scale, and then the changes on the modified or new mechanical function are considered, from which derive the use, potentially new. Therefore, an evolutionary teratology can be "adaptive" or not: there is no absolute generality; conclusions are determined case by case.

According to Guinard (2015), the application of teratology on an evolutionary scale allows discarding the normal/abnormal opposition and thus to consider both normality and abnormality in constant succession. The abnormality reflects a developmental anomaly that occurs at some point but then becoming "normal" later in evolution. Evolutionary teratology therefore includes a general state that is the recognition of a developmental anomaly by proportion, absence (loss of elements), increase (number of elements), identity transformation (homeosis), and whatever the degree is. Indeed, to take the example of the tetrapod limb, it is true that the loss of a phalanx is less impressive than a limb drastically reduced in size, but one must not fall into the trap of value judgment: each of these cases represents an anomaly, both legitimate and evolutionarily valid.

Specifically, a limb teratology is recognizable by (1) a remarkable disproportion of parts or the entirety of the limb and/or (2) by the absence or hypoplasia of a segment or a ray (Gold et al., 2011). The evolving framework implies to consider any anomaly identified as a malformation, the product of a developmental error (which is different from deformities that are the result of subsequent modifications to the initial development), and the anatomical criterion should be the basis as it is the only data available for fossils. As the classifications used in teratology are centered on the human species, due to the understanding of developmental and therapeutic issues, the nomenclature used by humans is appropriate to refer to patterns seen in other animals, combining principles from previous classifications (Frantz and O'Rahilly, '61; Burtch, '66; Day, '91; Gold et al., 2011):

(1) a generic title diagnosing the dominant limb anomaly, added, if necessary, with qualifiers specifying the intrinsic subvariations; (2) adding of a codification, if necessary, about the missing, additional, or affected elements according to the positions and orientations; (3) schematizing the recognized teratology/teratologies in a schematic model, which represents the last normal configuration in the evolutionary course.

The first example of an application of evolutionary teratology concerns the forelimbs of nonavian theropod dinosaurs of the family Tyrannosauridae and subfamily Carnotaurinae. The anatomy of these dinosaurs is particularly characterized by much shortened forelimbs, as shown by two iconic representatives of each group, *Tyrannosaurus rex* (70.6–66.043 Mya; Osborn, '05) and *Carnotaurus sastrei* (84.9–70.6 Mya; Bonaparte et al., '90). Figure 1 compares the morphologies of these two groups, relative to the reference pattern marking the last known changes in their phylogeny.

The evolutionary trend among Tyrannosauroidea shows a nonuniform shortening of the forelimb: it affected the humerus (and maybe radius and ulna) earlier in evolution, and only then affected the hand (Brusatte et al., 2010, 2011). Regarding digital reduction, a fourth metacarpal without phalanges is identified in *Guanlong wucaii* (161.2–155.7 Mya; Xu et al., 2006) and there are three metacarpals in *Dilong paradoxus* (130–122 Mya) whose third digit is slender but not reduced (Xu et al., 2004). As for Carnotaurinae, besides the fact that the basal Ceratosauria *Limusaurus inextricabilis* (161.2–155.7 Mya; Xu et al., 2009) has a much shortened forelimb with missing phalanges (Guinard, 2016), *Eoabelisaurus mefi* (Abelisauroidea, 175.6–167.7 Ma; Pol and Rauhut, 2012) shows that shortening began evolutionarily/phylogenetically with the distal elements—a pattern opposite to that of Tyrannosauroidea.

A common feature recognized on a global taxonomic assemblage (here, the theropods) that correspond to known teratologies of humans or other animals must meet a common diagnostic criteria. The study of fossil material, and its incomplete state, also imposes a constraint. An anatomical compromise must therefore be established to facilitate comparison among populations. Accordingly, an anterior micromelia among theropods—that is, severe shortening of the forelimbs—is identified when the humerus + radius + median metacarpal (or the dominant metacarpal) have a length of two-thirds (or less) of the femur. Figure 2 presents the result of this ratio for various taxa. The first diagnosis identified here is followed by a particular examination of each case. On the one hand, there is an overall conservatism in Tyrannosauridae, the anatomical pattern of the number of digital elements being the same (loss of all phalanges of digit III and a slender metacarpal III still present). The variation is observed in the relative limb proportion, with a global decrease in size following the sequence *Daspletosaurus* (70.6–66.043 Mya; Russell, '70), *Tyrannosaurus* and *Tarbosaurus* (70.6–66.043 Mya: Maleev, '74) (Fig. 2). On the other hand, there are clear variations in Carnotaurinae. Despite a shortening of the entire forelimb, plus additional shortenings of zeugopod and autopod, each taxon is not characterized by the same manual features. Figure 1 summarizes the information and the corresponding teratological nomenclatures.

Once this descriptive statement is achieved, the potential origins of these macroevolutionary changes can be investigated. Biology and developmental genetics then come into play, according to the principle of the evo-devo connection *sensu* Guinard (2012). Of course, these theropod dinosaurs are extinct. However, it is possible to use data from developmental biology to link teratological findings with such macroevolutionary changes. The reasoning is based on the general developmental processes that are evolutionarly conserved among vertebrates. For instance, it is known that the development of tetrapod limbs follows a common regulatory pattern (Shubin et al., '97) and the disruption of signaling pathways through genetic and epigenetic effects leads to abnormal limbs (Vogt and Duboule, '99; Shum et al., 2003; Al-Qattan et al., 2009; Huang and Hales, 2009; Lyons and Ezaki, 2009; Zuniga et al., 2012).

The regulation of the three major limb modules—stylopod (arm/thigh), zeugopod (forearm/leg), and autopod (hand/foot)—associated with *Hox* genes that specify their differences (Pratihar et al., 2010; Young et al., 2010) contributes to determine the evolutionary variability of the system. Variations in timing and expression of *Hox* genes can produce shortening of zeugopod and autopod and lead to loss of phalanges and nonossification of carpal elements (Favier et al., '96; Zákány et al., '97; Zakany and Duboule, 2007). The complexity of interactions and arrangement of *Hox* gene expression regions are a credible source to evolutionary micromelic variations of Carnotaurinae. It should be noted that the changes affecting regulators and factors may lead to decreases in the growth of limbs and loss of digital elements, which include, among others, *Shh* signaling, retinoids or the fibroblast growth factors (Niederreither et al., 2002; Moeller et al., 2003; Sagai et al., 2005; Yang and Kozin, 2009).

The conservatism of the evolutionary anterior micromelia in Tyrannosauridae suggests another developmental pathway. Variation in rates and growth processes—different forelimb/hindlimb timing relationship (Bininda-Emonds et al., 2007; Richardson et al., 2009)—are preferred by Guinard (2015) to explain the forelimbs shortening. As for the loss of the phalanges of digit III, according to him this reduction is associated with a change in the evolutionarily conserved *Shh* signaling, whose early termination leads to a truncation of the growth and differentiation of posterior digital rays (Wagner and Gauthier, '99). This scheme is consistent with the fossil record since the phalanges of digit III are still present ancestrally with the basal taxon *G. wucaii* (Tyrannosauroidea, 161.2–155.7 Mya) which still maintains a fourth metacarpal (Xu et al., 2006). This posterior digital reduction pattern is identified several times within

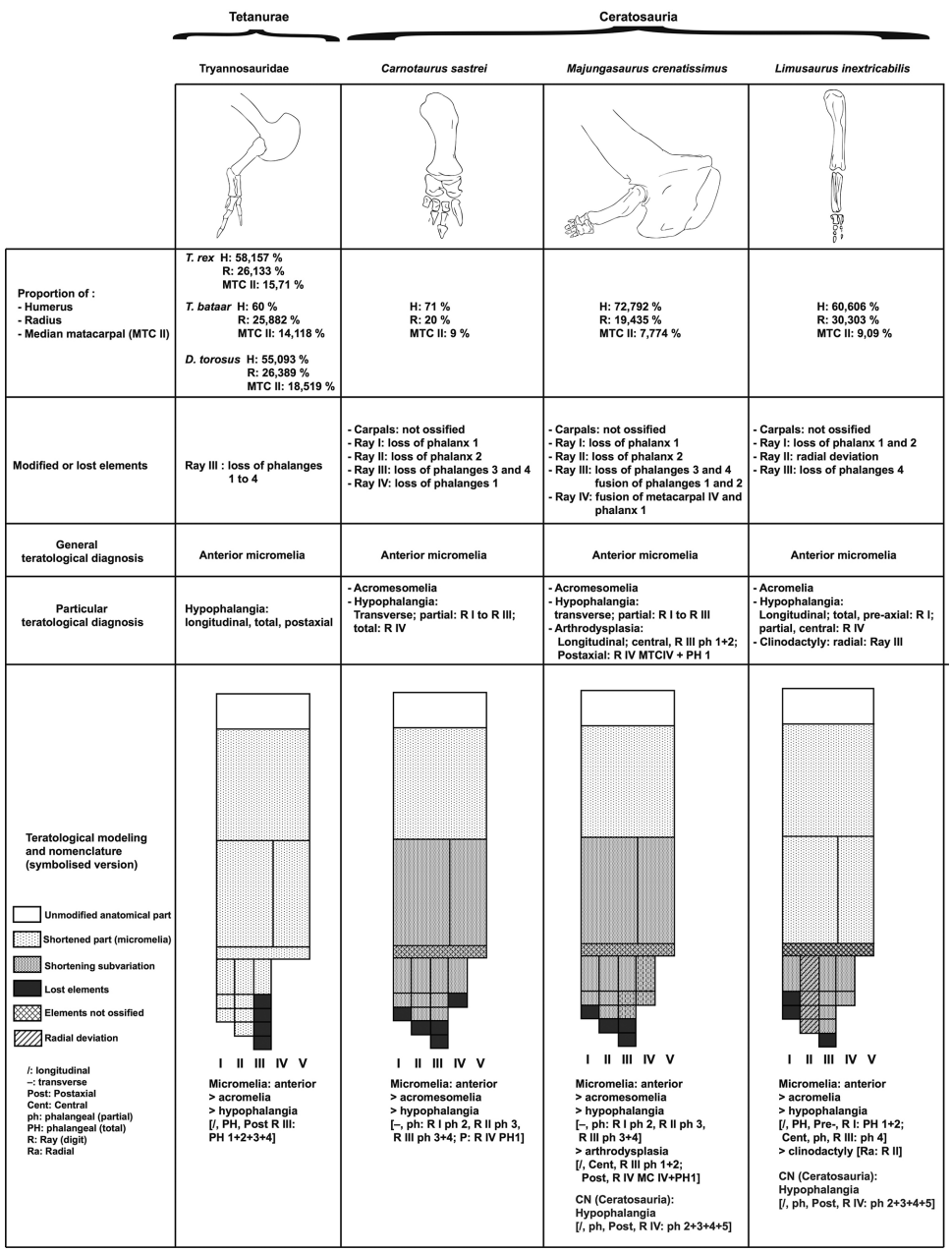

Figure 1. Forelimbs of Tyrannosauridae and Ceratosauria representatives with severe forelimb shortenings, along with anatomical anomalies and scheme of teratological identification and nomenclature (drawing of *T. rex* represents the Tyrannosauridae group). *Gorgosaurus libratus* and *Albertosaurus sarcophagus* are also concerned by the modeling and nomenclature of Tyrannosauridae. Not represented here, *Aucasaurus garridoi* (Carnotaurinae) exhibits other manual variations. CN is for complementary nomenclature for concerned taxa. Indeed, digit IV of Ceratosauria is not complete: it is a previous teratological feature persisting along the lineage and therefore that must be repeated for each taxon.variations; see Guinard (2015) for more details. CN is for complementary nomenclature for concerned taxa. Indeed, digit IV of Ceratosauria is not complete: it is a previous teratological feature persisting along the lineage and therefore that must be repeated for each taxon. See Guinard (2015) for more details.

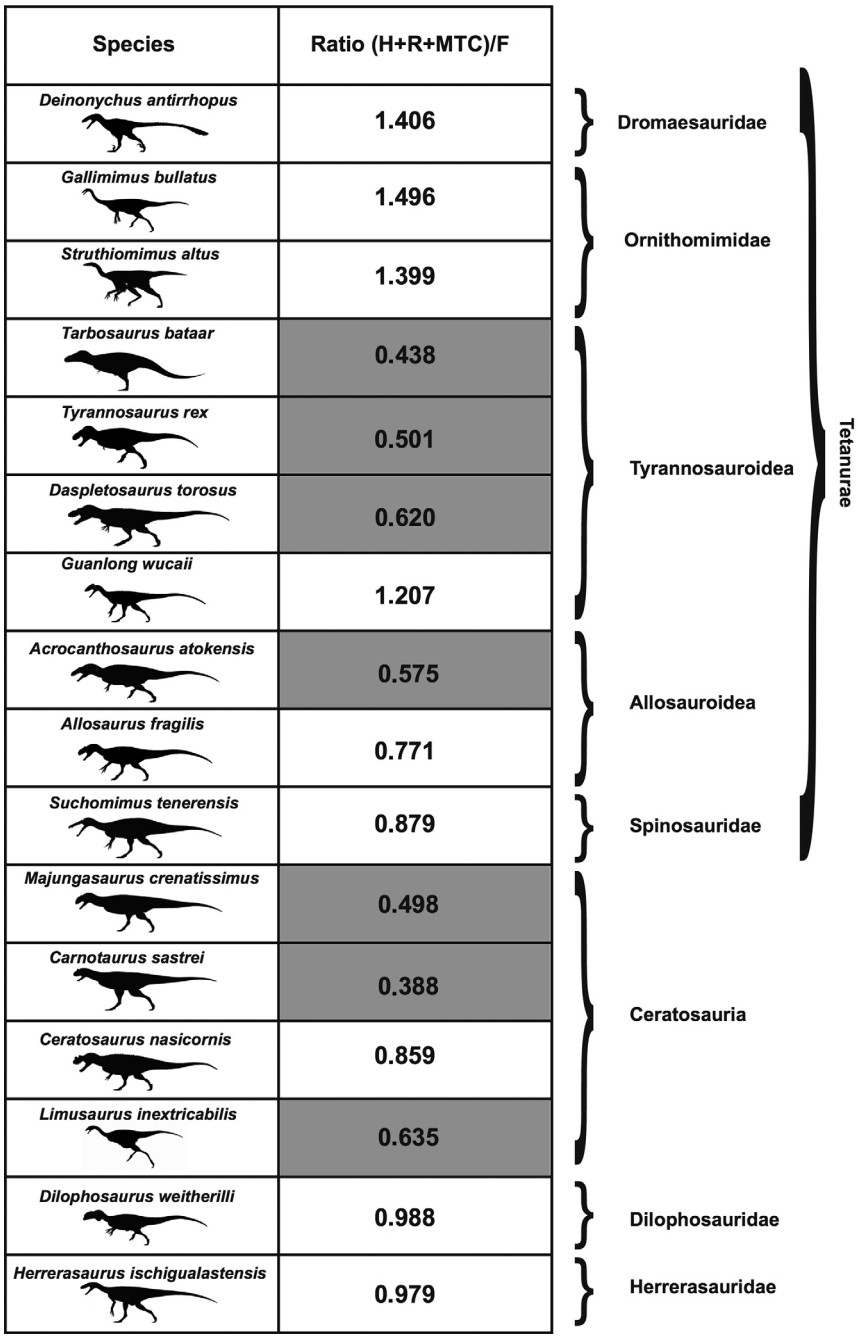

Figure 2. Ratio of comparison between forelimb length proportions (humerus, radius, median metacarpal) in relation with the length of femur among theropod dinosaurs. The shaded cells point species with an anterior micromelia (ratio of or under 0.66). Data used from Gilmore ('20), Alroy and Garcia Selles (2016) for *Ceratosaurus nasicornis*, Ostrom ('69), Alroy and Garcia Selles (2016) for *Deinonychus antirrhopus*, Osmólska et al. ('72) for *Gallimimus bullatus*, Maleev ('74) for *Tarbosaurus bataar*, Sereno et al. ('98) for *Suchomimus tenerensis* (metacarpal III used), Currie and Carpenter (2000), Alroy and Garcia Selles (2016) for *Acrocanthosaurus atokensis*, Middleton and Gatesy (2000) and Alroy and Garcia Selles (2016) for *Allosaurus fragilis*, Middleton and Gatesy (2000) and Bonaparte et al. ('90) for *Carnotaurus sastrei*, Brochu (2003) for *Tyrannosaurus rex*, Xu *et al.* (2009) for *Limusaurus inextricabilis*, Burch and Carrano (2012) for *Majungasaurus crenatissimus*, Xu X. (pers. commun.), Alroy and Garcia Selles (2016) for *Guanlong wucaii*, and Alroy and Garcia Selles (2016) for *Herrerasaurus ischigualastensis*, *Dilophosaurus weitherilli*, *Struthiomimus altus*, and *Daspletosaurus torosus*.

Tetanurae; Tyrannosauridae express an additional degree in this mechanism.

The second application of evolutionary teratology concerns avian manual digital identities, and specifically locating any teratological modifications at the level of the concerned phylogenetic nodes and taxa, following the last known modification principle (Guinard, 2015). Any change that is a developmental anomaly and expresses an incomplete structure should be repeated as many times as necessary in the phylogenetic succession. There has been controversy between paleontological and embryological data and the manual digit identities of birds and their tetanuran ancestors. Wagner and Gauthier ('99) proposed a principle of reconciliation with the frame shift, a homeotic transformation with identities of digits I–III developing on condensations II–IV, which is mechanically plausible (Vargas and Fallon, 2005; Vargas and Wagner, 2009; Larsson et al., 2010; Wang et al., 2011; Salinas-Saavedra et al., 2014). The phalangeal formula of *L. inextricabilis* contributed to emphasizing a hypothesis to define the digital identity of Tetanurae as II–IV (Xu et al., 2009). Nevertheless, following the framework of evolutionary teratology would contradict this hypothesis. This is because, according to Guinard (2016), *Limusaurus* and its manual evolutionary teratological features (reduced digits and acromelia, in addition of an anterior micromelia; Figs. 1 and 2) show an anatomical independence and separate potential developmental mechanisms compared to Tetanurae. That is, under this evolutionary teratological framework, one would support the principle of a frame shift regarding the identities of the manual digits I–III in the Tetanurae that did not occur in the Ceratosauria lineage.

DEVELOPMENTAL AND GENETIC WORKS AS CASE STUDIES

In conjunction with loci identified from human disease studies, deletion and mutagenesis screens in model organisms (*Drosophila*, mice, zebrafish) have allowed for the identification of genes required for normal morphogenesis, thus contributing to the rise of evo-devo (Gilbert and Epel, 2009; Mallarino and Abzhanov, 2012). Specifically, genes and pathways that have been identified *a priori* as having a role in the morphogenesis of a homologous tissue or structure of interest in a "nonmodel" species have been explored and functionally challenged to begin to dissect how diverse morphologies arise in nature. Utilization of NGS technologies on tissue samples for genes being actively transcribed (RNA-Seq) provides an unbiased approach for identification of genes with a direct function in tissue morphogenesis without the need for a sequenced genome (Pantalacci and Semon, 2015). However, given the importance of organisms for exploring gene function and cellular dynamics during morphogenesis and disease in humans, one avenue of evo-devo that needs to be further explored is the use of phenotypes found in nonhuman taxa—including both the wild-type configuration and the anomalies found in the members of those taxa—that are phenocopies (*sensu* Goldschmidt: see section Intellectual Connections and Broader Evolutionary Implications) of congenital anomalies found in humans and/or other taxa (Fig. 3).

In tetrapods, studying the appendicular system conveys the mode of organismal locomotion and provides hints to the ecological niche used by an organism, whereas the craniofacial system presents a species' mode of feeding, dependence on different sensory systems, protects the brain, and may also be a site for visual communication (Hildebrand et al., '85; Hanken and Hall, '93a, '93b, '93c, Schwenk, 2000; Hall, 2007). The architecture of the limbs and craniofacial complex are homologous across tetrapods and thus are constructed using the same embryonic tools, with differences in gene regulation giving rise to the tremendous diversity observed in nature (Hanken and Hall, '93a, '93b, '93c; Schneider et al., '99; Hall, 2003b; Carroll et al., 2004). In the following paragraphs, a few examples are presented that highlight morphological diversity in craniofacial and limb development in nature and present one of many phenotypes across the morphospace of limbs and cranium (see Hallgrimsson et al., 2015) that phenocopy specific human congenital malformations structurally and/or due to the developmental pathways perturbed. As Figure 3 shows, not only are signaling pathways conserved in the construction of body plans (limbs and craniofacial elements), nonhuman species are also susceptible to developmental anomalies that parallel human diseases/syndromes such as midfacial patterning defects and limb reductions, losses, and duplications. Importantly, within the developmental perspective of evo-devo-path, studying natural systems allows researchers to understand morphogenesis within the context of natural selection (as the "tinkerer") rather than an anomalous element with limited or no function.

The first example concerns *interdigital webbing*. For instance, aquatic birds like ducks retain interdigital webbing between their hind digits, and in their specific case this configuration is seemingly useful for propulsion through an aquatic environment (also convergent in aquatic frogs). Similarly, bats retain interdigital webbing in their hands and they propel themselves through the air for powered flight. The web footed gecko of the Namib desert presents interdigital webbing that might help to support the lizard as it moves across the fine sand, while most tropical salamanders of the family Plethodontidae retain interdigital webbing. However, one needs to be very careful about the possible adaptive gains of these features; for instance, regarding the salamanders the supposed evolutive value of the webbing as adaptive aid for walking on smooth surfaces has been challenged (see Alberch, '81; Jaekel and Wake, 2007; Adams and Nistri, 2010).

In all these cases, the embryonic webbing is retained in these species and represents a form of adaptive syndactyly where adjacent digits are joined by interdigital epithelium and mesenchyme, which is typically lost through apoptosis at later stages of embryonic development once digits and phalanges have been

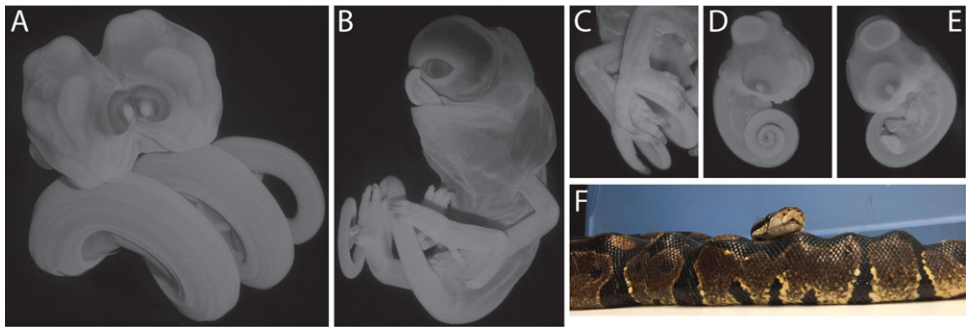

Figure 3. Anomalies present in squamate reptiles that have also been identified in humans, underscoring natural and malformed reptiles as models for human diseases (mutant embryos were harvested during normal lab activities not induced through mutagenesis). (A) Dicephalic African House Snake (*Boaedon fuliginosus*), generally due to excessive hedgehog signaling along the anterior embryonic midline, in contrast to a (B) Cyclopic (Holoprosencephalic) Veiled Chameleon (*Chamaeleo calyptratus*) whose deficiency is generally due to an absence of hedgehog signaling along the anterior midline. (C) Unilateral polydactyly and an ectopic limb branching from the knee of the same cyclopic individual. (D) Amelia of fore-and-hind limbs (phenotypically very snake like) while (E) shows Amelia of the forelimbs only. (F) A putative Ball Python (*Python regius*) model displaying an ALS (Amyotrophic Lateral Sclerosis, Charcot's Disease, Lou Gehrig's Disease) phenotype.

patterned (Zuzarte-Luis and Hurle, 2005; Zeller et al., 2009; Hernandez-Martinez and Covarrubias, 2011). *Fgf8* is generally utilized as a survival factor (retained on axis of the digits) and Bmp signaling is a proapoptotic signal present in the interdigits (Diaz-Mendoza et al., 2013; Diaz and Trainor, 2015). Inhibiting interdigital Bmp signaling in a "webbing free" species like a chicken hindlimb through the introduction of a dominant negative Bmp receptor led to a retention of embryonic interdigital mesenchyme reminiscent of the duck foot and bat hand, for which the latter species inhibit Bmp signaling through heterotopic expression of the Bmp antagonist gremlin in the interdigital mesenchyme (Zou and Niswander, '96; Weatherbee et al., 2006).

Importantly for the context of evo-devo-path, recent work on an emerging evo-devo model organisms, the veiled chameleon, has showed that aside from both autopodia (hand/foot) having a midline split, syndactyly also plays a role in the formation of the derived autopodium by forming two clusters of digits on each limb, which vary in the digits that are bound in syndactyly (Fig. 3C). In the hand, the clusters are digits (I,II,III)|(IV,V), whereas in the foot the digit bundles are (I,II)|(III,IV,V), where "|" denotes the cleft location between digits. Inhibition of Bmp signaling in both the bat and duck interdigit mesenchyme by heterotopic expression of Gremlin led Diaz and Trainor (2015) to take the candidate gene approach and look for ectopic mRNA expression between digits bound in syndactyly. While gremlin was expressed normally in the developing autopodia, no ectopic gremlin expression was observed and the mechanism of interdigit webbing retainment remains unknown and in need of further study in chameleons.

In humans, syndactyly of the limbs is one of the most common hereditary defects with a prevalence of 3–10 (and up to 40) per 10,000 live births (Malik, 2012; Stevenson and Hall, 2016). Syndactyly may occur unilaterally, bilaterally, in isolation or as part of a syndrome (Schwabe and Mundlos, 2004). Given the importance of *gremlin* as a *Bmp* antagonist in the evolution of interdigital webbing, only recently was a human limb malformation (nonsyndromic Cenani–Lenz type syndactyly) identified, which involved a duplication of the *Gremlin 1-Formin 1* locus and phenocopied the Bmp antagonized chick limb (Dimitrov et al., 2010). Thus, animal models have shown the importance of pathways in limb morphogenesis in natural variants as well as through genetic perturbation prior to the identification of mutants in humans. Other genes and pathways involved in human cases of syndactyly are *HoxD13*, *FBLN1*, *LMBR1*, *LRP4*, and *Jag2* (Schwabe and Mundlos, 2004; Malik, 2012; Pinero et al., 2015).

Another example concerns the split hand/split foot malformation (SHFM). While only a few tetrapods have been the source for our knowledge of how limbs develop, all members of this lineage build the diversity of limbs utilizing the same conserved genetic circuitry with regulatory modifications driving morphogenetic divergence. It must also be added that nonhuman tetrapods are also able to develop equivalent congenital malformations. SHFM (i.e., ectrodactyly and lobster claw) is a rare human disease, with an incidence of 1:90,000 live births for the typical phenotype (absent or reduced middle finger) and 1:150,000 for atypical (a more severe case with more digits reduced or missing). The phenotype of patients is the presence of a midline cleft (of varying size) surrounded by varying numbers of digits, which are

generally bound by syndactyly. SHFM may be present bilaterally as well as on the hands/and or feet in isolation or as part of a syndrome and has been identified in dogs, cats, cows, chickens, frogs, rabbits, and manatees (see references in Duijf et al., 2003).

The human syndrome is classified into six different types with only general chromosomal regions having been mapped for a majority of the cases, the most common nonsyndromic form being SHFM type-1 associated with variable deletions in chromosome 7q21. The region most commonly affected spans *Dlx5* and *Dlx6* genes, both expressed in the apical ectodermal ridge (AER) of the growing limb bud, with other genes identified being *Wnt10B*, *Tp63*, *Wnt5a*, *Ror2*, and *Dactylin* (Duijf et al., 2003; Conte et al., 2016; Proudfoot et al., 2016; Stevenson and Hall, 2016). Recent work identifying the role of *Wnt5a* in SHFM has shown the importance of the noncanonical PCP *Wnt* pathway in establishing basolateral and planar cell polarity to the AER, thus promoting a role in the maintenance of the AER rather than the initial establishment for this source of *Fgf8* and *Dlx5/6*. *Dlx5/6* double knockout mice were partially rescued through culturing with exogenous *Wnt5a* (Conte et al., 2016), which restores the AER. All identified genes are involved in the maintenance of the AER either through the maintenance of the SHH signaling pathway, BMP antagonism through *Grem1-Fmn1*, and continued expression of *Dlx5/6* and *Fgf8* in the AER (Duijf et al., 2003; Conte et al., 2016).

While SHFM is a very extreme phenotype with modification of the entire autopodium, it is difficult to imagine a tetrapod with such a phenotype being adaptive. Diaz and Trainor (2015) used the veiled chameleon to study cleft formation and found that unlike all current models establishing the loss of the AER (and *Fgf8* expression), chameleon cleft formation occurs despite a normal expression pattern of *Fgf8* along the AER. Patterning was also normal with *Shh* expression in the zone of polarizing activity and the presence of five digits with a full complement of phalanges. As mentioned previously, syndactyly was also associated with the chameleon cleft phenotype; whether they are mutually exclusive remains to be determined. Antagonizing Bmp expression by exposing limbs to Dorsomorphin *in vitro* prior to cleft formation inhibited hand and foot splitting, thus supporting the role of Bmp signaling in the process of cleft formation (most likely through increased interdigital cell death), though a physical musculoskeletal mode of splitting remains to be tested. In addition, chameleon wrists and ankles have varying degrees of fusions of carpal and tarsal elements along with differential growth in the size of these mesopodial elements, which correlate with differences in distal placement of the metacarpals/tarsals and digits. A survey of mesopodial element variation in patients with SHFM has not been conducted to the authors' knowledge and would be of interest if the more proximal skeleton can have a significant impact on distal development of the hand and foot skeleton as was observed in the chameleons. Figure 10E and F of Diaz and Trainor (2015) presents a patient with SHFM whose midline carpals appear to have fused into a larger element at the site of clefting (X-rays of human patients generally being conducted prior to mesopodial ossification so are not very visible).

The third example concerns *craniosynostosis and suture patency*. The craniofacial system is the most complex structure on the vertebrate body, being derived from both endoderm, ectoderm (neural and nonneural), mesoderm, and neural crest cell embryonic tissue (Santagati and Rijli, 2003; Minoux and Rijli, 2010). Specifically, the skeleton plays a crucial role in protecting the underlying brain and sensory systems and displays a very tight relationship with the underlying meningeal membranes and brain to allow for proper cranial growth (Richtsmeier et al., 2006; Siegenthaler and Pleasure, 2011; Richtsmeier and Flaherty, 2013). The broad thin plates of bone forming the skull (calvaria) are derived from both neural crest cells (anterior) and mesoderm (posterior cranium), thus the skull roof has a dual origin (Gross and Hanken, 2008). The intervening sutures separating the cranial bones are also sites for cells that proliferate and contribute to the growing osteogenic fronts of the calvarial bones (Rice and Sharpe, 2008; Zhao et al., 2015). Sutures remain as dense connective tissue (patent) and, depending on the species, differentially ossify and erase the connective space between two bones and leads to the fusion of two bony plates. Premature fusion (ossification) of sutures leads to craniosynostosis, one of the most common craniofacial anomalies in humans with an incidence of 1: 2,500 live births (Rice and Sharpe, 2008; Muenke et al., 2011). Several pathways have been identified in the loss of suture patency and appear to be different across sutures, primarily FGFR1-3, *Twist1*, *EphrinB2*, TGFßs, and Bmps (reviewed in Rice and Sharpe, 2008; Beederman et al., 2014).

While premature fusion of calvarial bones across sutures due to loss of patency leads to a constraint on cerebral expansion and ultimately neurological problems and abnormal cranial skeletal growth, when observed in an evolutionary framework for tetrapods several lineages have undergone trends cranioskeletal simplification due to the loss and/or fusion of calvarial bones ("Williston's law"; Gregory, '35; Sidor, 2001; Depew and Simpson, 2006; Richtsmeier et al., 2006; Esteve-Altava and Rasskin-Gutman, 2015). Recent work exploring mammalian fossils and extant mammals has highlighted the continued presence of the postparietals (interparietals) and tabular bones of the posterior cranium (the latter having been considered to have been lost in modern mammals; Koyabu et al., 2012). Embryonic fusion of early calvarial condensations across a developing suture is a direct way to simplify the number of cranial bones present and is equivalent to an evolutionary craniosynostosis. Recent work in our (Diaz) lab supports the presence of a distinct ossification center in squamate reptiles, which correlates with a postparietal and the possibility of a distinct tabular as had been described in Koyabu et al. (2012), though a transient postparietal in an alligator had already been described by Klembara (2001). Thus,

the process of premature fusion of calvarial bones across sutures is a fundamental process reiterated through the evolution of the cranioskeleton. Identification of genes whose regulation has been modified in patent versus synostosing sutures in reptilian taxa (through RNA-Seq data collection) may provide new genetic players that may also be altered in human patients. The examples and discussion presented in this section thus stress the importance of using current genetic and developmental knowledge and techniques, that is, a modern "devo" approach, in order to study the mechanisms that differentiate normal and abnormal ontogeny in humans and other organisms, and thus to reach a more comprehensive understanding of the links between macroevolutionary changes, development, and pathology.

HUMAN PATHOLOGY AND DEVELOPMENT AS CASE STUDIES

A major particularity of evo-devo-path is that this subfield of evo-devo aims to bring back the notion that humans themselves can, and should, be a key case study in works and discussions on normal and abnormal development, as was proposed and done centuries ago by authors such as Étienne and Isidore Geoffroy Saint-Hilaire (see section Brief historical Introduction to Studies on Links between Evolution and Developmental Anomalies). This point contrasts, for instance, with the main direction that developmental biology and evo-devo have been taking in the last decades, which is to essentially use nonhuman model organisms to compare normal and abnormal development and subsequently potentially discuss the possible mechanisms/patterns related to particular human evolutionary and pathological phenomena. This issue was recently reviewed by Diogo et al. (2015a), Diogo (2016), and Diogo et al. (2016), who defined evolutionary developmental pathology and anthropology (evo-devo-P'Anth). As its name indicates, the main difference between evo-devo-P'Anth and evo-devo-path is that apart from focusing on human pathologies as a case study per se—as does evo-devo-path (Diogo et al. 2015a, 2015b, 2015c)—evo-devo-P'Anth in addition also pays a special attention to data obtained from biological and physical anthropology. For instance, it pays attention to information on the specific evolutionary changes, including convergences, parallelisms, and reversions of the muscles in each major extant primate group, and to the evolutionary rates within these transformations (e.g., Diogo and Wood, 2011; Diogo and Wood, 2012a; Diogo and Wood, 2012b; Diogo and Wood, 2013; Diogo and Molnar, 2016; Diogo and Wood, 2016).

Diogo et al. (2015c) is an illustrative example of an evo-devo-path work because it used a new tool that incorporates elements of mathematical network theory, systems biology, evolutionary biology, and anatomical sciences-anatomical network analyses-to empirically study and discuss the links between evolution, development, and pathology. We will not describe the methodology employed in anatomical network analyses in detail here, as that has been done in various recent papers (e.g., Esteve-Altava et al., 2013; Esteve-Altava et al., 2015). The example shown in Figure 4 will suffice to show the potential of this methodology and illustrate an extreme case of developmental constraints that strongly supports Alberch's logic of "monsters" (see section Brief Historical Introduction to Studies on Links between Evolution and Developmental Anomalies). Anatomical network analyses of the muscles and their contacts in the most common, so-called "normal", configuration of the adult human head have revealed that there are three main muscular modules: an "ocular/upper face" module including facial muscles of both the left and right sides of the head, a "left orofacial" module including left facial muscles, and a "right facial" module including right facial muscles (Fig. 4, left; Esteve-Altava et al., 2015). The same modules are also found in human newborns (Fig. 4, middle). Strikingly, in an extreme case of congenital malformation seen in a cyclopic human fetus with trisomy 18 (described in detail by Smith et al., 2015), the very same three muscular modules are present despite the severity of the head defects and the cyclopic condition, showing that there is in fact a "logic" (order) even in such cases of extreme developmental deformities (Fig. 4, right).

Anatomical, neurological, and pathological studies of humans further support the idea that these particular facial muscle modules are in fact deeply entrenched in the evolution, development, and overall organization of our heads. For instance, studies in humans and nonhuman primates suggest that the innervation of the face is bilaterally controlled for the upper part and mainly contralaterally controlled for the lower part and, accordingly, in humans paralysis of the upper face is often bilateral while of the lower face is often unilateral (Müri, 2016). This is in line with the facial muscle modularity revealed by our network analyses (Fig. 4). Recent studies on modularity, for instance about the modular heterochrony of dermal versus endochondral bones, have also provided examples of strong internal constraints, and pointed out how in many cases such constraints can have a crucial role in vertebrate macroevolution (Koyabu and Son, 2014; Koyabu et al., 2014).

Diogo and Wood (2012b) defended the idea that reacquisition of adult morphological structures that were missing in their adult ancestors for long periods of time is possible since the associated developmental pathways were kept in their evolutionary history, for example, at least in early developmental stages. For instance, chimpanzees display a reversion of a synapomorphy of the Hominidae (great apes and modern humans; acquired at least 15.4 Mya ago) in which adult individuals have two muscles contrahentes digitorum—one going to digit IV and the other to digit V—other than the muscle adductor pollicis, which is the only contrahens muscle present in adults of other hominid taxa, including humans. Developmental studies of hand muscles (e.g., Cihak, '72) showed that karyotypically normal human embryos do have contrahentes going to various fingers, but these muscles are then usually reabsorbed or fuse with other structures during later embryonic development. Furthermore, in

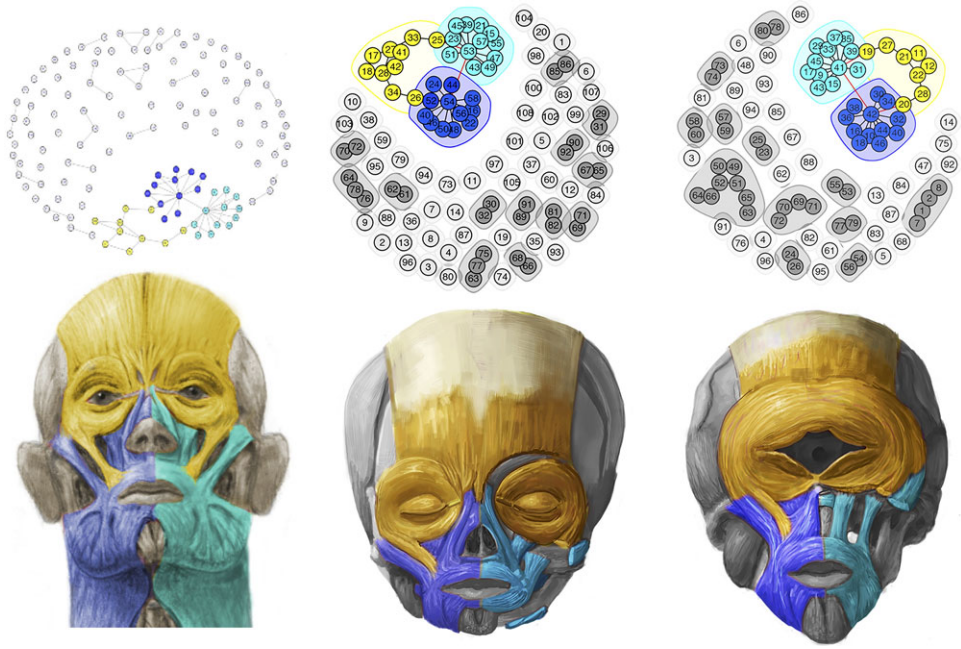

Figure 4. Modules obtained from anatomical network analysis of head and neck muscles of normal configuration seen in human adults (left) and newborns (middle) and of a cyclopic human fetus with trisomy 18 (right) (modified from Esteve-Altava et al. (2015) and Smith et al. (2015)). For the purpose of the present paper, it is not needed to repeat all the information regarding which structure corresponds to each number shown in the top of the figures, as the key is given in Esteve-Altava et al. (2015) and Smith et al. (2015): it suffices to note that the numbers refer to musculoskeletal structures and the links (i.e., contact or articulation between bones, muscle fusions, or muscle–bone attachments) between them form the respective networks. Note that, despite the severity of the cyclopic trisomic phenotype, the three muscular modules are exactly the same in all three conditions, that is, there is always (1) an "ocular/upper face" module including facial muscles of both the left and right sides of the head plus (2) a left "orofacial" module and (3) a right "orofacial" module, both including also facial muscles.

karyotypically abnormal humans, such as those with trisomies 13, 18 or 21, the contrahentes often persist—as "atavisms"—until well after birth (e.g., Smith et al., 2015).

This subject is related to a key concept for evo-devo-path: atavisms, which 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 ('72) showed that the intermetacarpales are also present as discrete hand 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. For recent works on atavisms concerning skeletal, instead of muscular, atavisms, see Senter and Moch's (2015) paper and references therein.

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 development, so that if faced with external perturbations (e.g., climate change, habitat occupied by new species) evolution can use that potential (adaptive plasticity *sensu* West-Eberhard, 2003). However, for authors such as Gould, ('77, 2002) and Alberch ('89) the occurrence of such cases supports a "constrained" (internalist) rather than an "adaptationist" (externalist) view of evolution. It is possible that the *tendency to accumulate hidden variation* could have been the outcome of the evolutionary success that plasticity confers in many situations. However, one cannot say that the *persistence of specific, individual atavistic structures*—such as the muscle platysma cervicale (see Fig. 5) in early human development (Gasser, '67)—that then

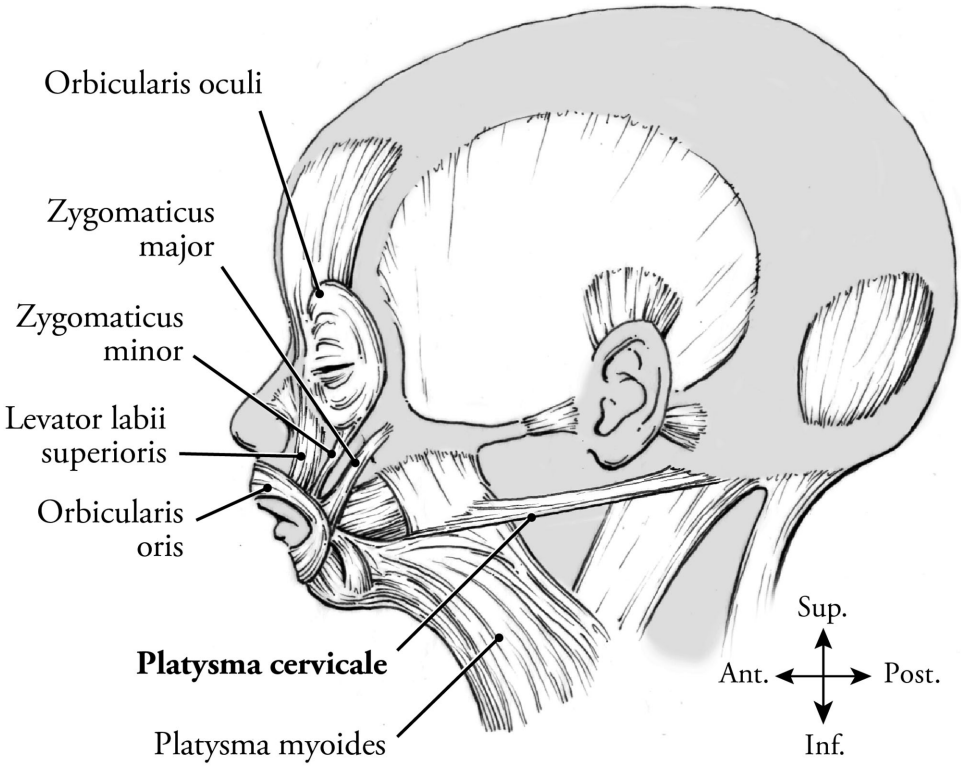

Figure 5. Platysma cervicale, an atavistic muscle sometimes present in modern humans, here originating from the posterior platysma myoides and inserting with the sternocleidomastoideus onto the mastoid process; anomalies labeled in bold (modified from Smith et al. 2015).

normally disappear during development is a phenomenon that is associated with specific positive selective forces (Diogo et al., 2015b).

That is, nature cannot guess the future, and thus cannot predict whether the platysma cervicale might be something that will be "useful" in the future of humanity. Instead, the platysma cervicale is kept during early human ontogeny due to evolutionary/developmental constraints, and the occurrence of such constraints is what may lead, in the future, to an eventual phylogenetic reversion in which adult humans may normally have that muscle. In fact, one has to keep in mind that apart from phylogenetic reversions, there are other types of reversions, for example, the so-called "Lazarus developmental reversions" *sensu* Minelli (2003, 2009). These are features that disappear from an organism's body at a given developmental stage, and then reappear at a later stage. An example given by Minelli concerns the fourth pair of legs in the mites: the legs are present in the embryo, lacking in the larval instar, and then present in the nymphal and adult stages of most mites. 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 as predicted by Haeckel's recapitulation: they correspond instead to the muscles of the *embryos* of those taxa (Diogo and Wood, 2012a, 2012b). The developmental pathways resulting in the presence of these muscles in adults of those taxa were not completely lost in modern humans, even after several million years, likely because these pathways are associated (e.g., pleiotropy) with those recruited in the formation of other structures that *are* present and functional in modern human adults.

A famous case of potential human "atavism," which was proposed by Darwin and many other 19th-century authors, is the presence, in some human newborns and even adults, of a tail-like appendage at the level of the coccyx or lumbar spine (Fig. 6). Authors such as Verhulst (2003) attacked that idea by arguing that these appendages are very different from animal tails, for example, they almost never contain bones (vertebrae) or cartilage. However, it should be noted that there are reports of muscles associated with these human tail-like structures, which do resemble caudal muscles of other animals (e.g., Weidersheim, 1895). In fact, it is now becoming clear that many

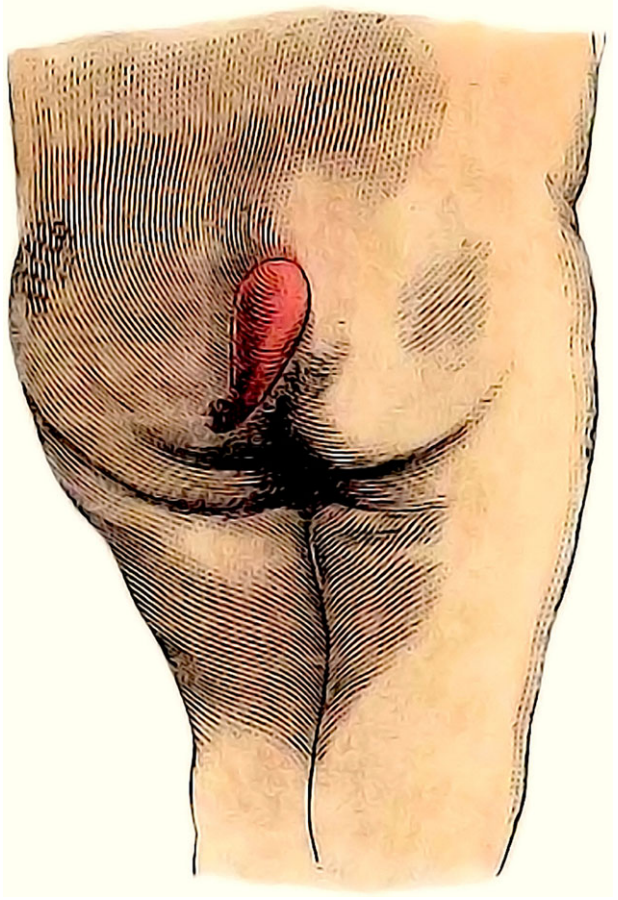

Figure 6. Human tail connected to the coccyx, modified from Bartels (1880–1881).

of the human "tails" described so far are true tails, as recently noted by Tubbs et al. (2016). During weeks 4–6, human embryos normally have tails with 10–12 caudal vertebrae and a distal portion containing mesodermal elements and lacking bone. By the end of the fifth week, the tail is at its maximum relative length, measuring about one-sixth of the length of the whole embryo. By the eighth week, the tail becomes normally fully diminished, that is, the distal coccygeal segments become phagocytosed by white blood cells while the surrounding vertebrae undergo reduction, and the cells of the distal mesodermal, nonbony portion also become phagocytosed (Tubbs et al., 2016).

However, in a few humans an appendage persists until later developmental stages, including adulthood, as a result of the disturbance of the normal regression of the embryonic tail: those are the cases that can be classified as a true human tail, as proposed by Tubbs and colleagues. Remarkably, in some cases reflex, associated with crying or coughing, or even voluntary movement, associated with the presence of voluntary muscles, of the tail has been reported (Tubbs et al., 2016). If we keep in mind that tails disappeared phylogenetically more than 10 million years ago and that they are not present in adults of any hominoid (humans + apes) extant taxon, the presence of such true tails in a few humans is truly impressive, and reminds us again of how profoundly constrained evolution, as well as both normal and pathological development, are.

INTELLECTUAL CONNECTIONS AND BROADER EVOLUTIONARY IMPLICATIONS

In the past decades, there has been a renewed scientific interest in the links between development, macroevolution, and pathology, in particular since the works of Frietson Galis, who should probably be considered the "mother of modern evo-devo-path." This is because she combined macroevolutionary and developmental studies with pathological studies that also included humans as a key case study, for instance, concerning anomalies of the cervical vertebrae and their possible links with cancer (Galis, '99). Galis' works were in particular important to empirically show, using such human pathologies, the difference between two major types of internal factors. One is *internal constraints sensu* Gould and the physicalist framework of authors such as Newman. These constraints are mainly related with the conservation of developmental genetic/epigenetic mechanisms and with the physical proprieties of tissues themselves, resulting in significant unfilled regions of the morphospace (Olson, 2012). The other is *internal selection*, as shown, for instance, by the death of human fetuses with more than seven cervical vertebrae because of a general disturbance of the phylotypic stage, that is, where the morphospace can be/is filled, but then internal factors lead to death still in early stages of development (Galis, '99). Specifically, Galis ('99) 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 high number of cervical vertebrae very likely perturb sensitive early stages of development such as the "phylotypic stage," leading to major abnormalities.

As put by Wagner and Schwenk (2000: 157), internal selection is "independent of external, environmental selection pressures (because the limitations are imposed by intrinsic attributes of the organism)"; as such, it is the internal coherence and functionality of the system, as a whole, that imposes its own 'internal selection' on individual characters, determining which character variants are viable." One of the links between the case studies discussed in the three sections above is that they are related to both internal constraints—in the sense that they often lead to similar phenotypic outcomes in different lineages—and internal selection—in the sense that changes in this type of selection are the ones that explain why some organisms cannot reach

adulthood after a certain level of disturbance leading to a certain phenotype, while others succeeded to do so during evolution and currently have that same phenotype as their wild-type configuration.

In his book *Genetics, Paleontology and Macroevolution*, Levinton (2001) subsequently 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, for instance, 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 case studies supporting an internalist view of evolution and some points of the logic of "monsters," but stressed that development is, nevertheless, probably more variable than defended by Pere Alberch. It should however be emphasized that not all major macroevolutionary changes in ontogenetic trajectories occur via the phenomenon that is mostly emphasized by Gould and Alberch, that is, heterochrony. Some authors argue that heterotopy—changes in the place (as opposed to the time) of action of genes—could be even more important at a macroevolutionary scale (e.g., Schlichting and Pigliucci, '98). One example that these authors provide refers to Carroll et al.'s ('95) study on *Drosophila*. The wings in pterygote (winged) insects originate from a segment of the leg, and fossil evidence suggests that early winged insects had wings on all thoracic and abdominal segments (Fig. 7). Carroll et al.'s study showed that a series of homeotic genes repress wing formation instead of promoting it. The phenotypic effect of knocking out these genes was the appearance of more wing primordia, showing how heterotypy—genes that are not expressed in some of the segments—can be related to a major macroevolutionary trend in invertebrates.

More recently, Weisbecker and Nilsson (2008) provided a further example of how wildtypes of current taxa that can be seen as Goldschmidt's hopeful "monsters," which is somewhat similar to some of our own case studies, discussed in the three sections above. The example concerns a group of marsupials that have syndactyly (fusion) of digits II and III as the normal phenotype, and that were even called "Syndactyla" for some time, a group nowadays often considered to be nonmonophyletic. As noted by these authors, such cases of syndactyly are probably the subject of homoplasy in marsupials and may well be due to nonadaptive traits related to the integration of digit elements through ontogenetic constraints. That is, syndactyly would only represent the loss of a single digit, rather than the incapacitation of both digits as in soft tissue syndactyly of the human hand. In contrast, in functional syndactylous digits the net loss of a single digit may have had a mild impact, compared to a loss of flexing capacity, as is the case in syndactylous human hands. According to them, this may have aided the spread of marsupial syndactyly through the ancestral populations, that is, it would be essentially a neutral feature in this respect, and not detrimental as in human syndactyly. That is, they hypothesize that there was probably a rapid origin of fully integrated, and as such fully functional, syndactylous digits in marsupials, and argue that this would also explain the lack of intermediates of syndactylous feet in extant or fossil marsupials and the heterochrony observed in their study. In fact, they noted that similar scenarios have been argued for other cases such as the origin of bat wings, as these scenarios would explain the conservative size relationship of digits across bat species and also the lack of

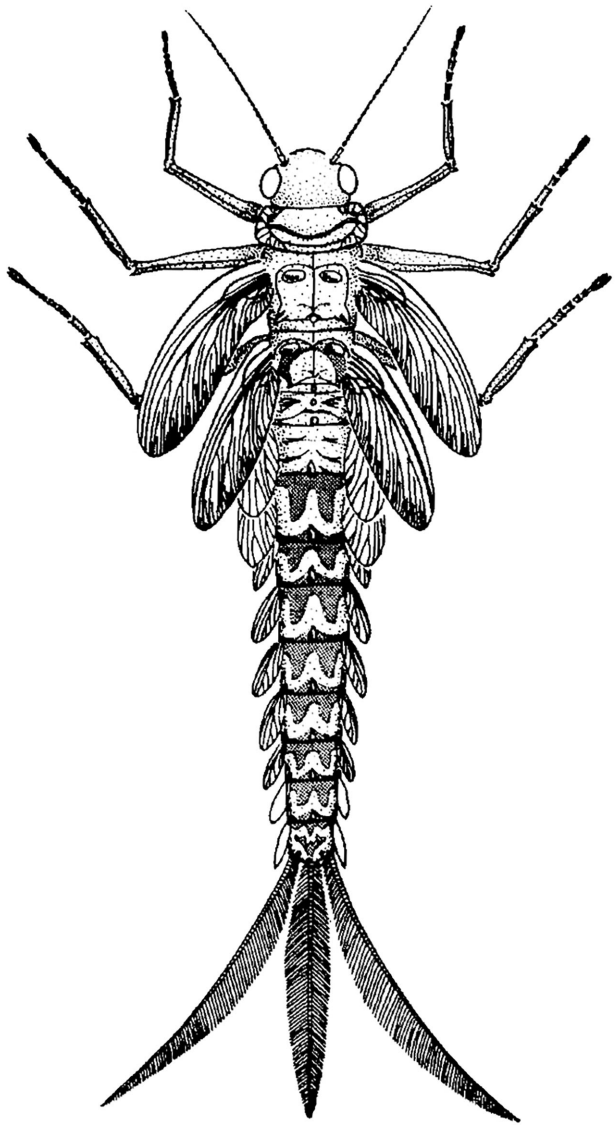

Figure 7. Paleozoic mayfly nymph (*Kukalova americana*; modified from Kukalova-Peck ('85)).

fossil intermediates of bat wings with a localized change in Bmp expression patterns.

Regarding macroevolutionary case studies that also include a strong paleontological component and that provide strong theoretical and empirical support for the importance of hopeful "monsters" for evolution, and in particular for macroevolution and the origin of new body plans, these can be found, for instance, in Raff's ('96: 189) book *The Shape of Life*. One of the many examples concerns the importance that homeotic transformations seem to have played in the evolution of insect body plans, an issue briefly mentioned above. The Diptera and Strepsiptera have a single pair of wings and a pair of halteres. In dipterans, the wings are on the second thoracic segment and the halteres on the third, while in strepsipterans the main wings are on the third and on the second there are shortened forewings that, according to Raff, correspond to/derive from dipteran-like halteres. As noted by him, it is possible that the *Ubx* gene, which is expressed in the *Drosophila* third thoracic segment, might be expressed instead in the second thoracic segment of strepsipterans. Such a change could very well not be detrimental, that is, having wings and halteres in the second and third versus third and second segments can be mainly a functionally neutral change, for instance. Thus, a homeotic transformation occurred by chance could have lead to a different form and ultimately to the existence of a new higher clade. Raff provides numerous similar examples in his book, particularly from insects.

Raff therefore argues that the concept of a developmental body plan rests upon the communality of developmental patterns leading to a finished adult structure. This communality of organization would be related to the occurrence of a mainly constant phylotypic stage because the internal mechanisms of development allow no other way to build a certain body plan. Then, within this communality, single switch gene determination or developmental modules can occur at various points in development. An example, among many others, is that ectopic expression of the *nanos* gene product in the anterior end of a *Drosophila* embryo causes the formation of a second abdomen. According to him, substantial evolutionary modification can thus take place through small changes in existing gene networks, without reinventing the basic components, cell types, tissues, and organs of the body of organisms. For instance, the expression of *wingless* in a segmentally iterated manner in *Tribolium* embryos, and the fact that the *wingless*-expressing cells lie in the same relationship to *engrailed*-expressing cells as in *Drosophila*, suggesting a long-conserved mechanism of gene expression as well as a conserved pattern. Therefore, Raff pointed out that—as explained above and shown in Figure 7—in plesiomorphic Paleozoic insects leg and wing primordia might have arisen in all thoracic and abdominal segments and the wing primordia migrated dorsally as they do in dragonflies, and that the adult would have had legs and wings on all body segments. Then, as Paleozoic insects evolved further, there was an evolutionary trend toward the predominance of thoracic legs and wings, the suppression of abdominal legs and wings being controlled by the homeotic genes of the *Antennapedia* and *Bithorax* complexes (see also notes on heterotopy, above).

As argued by Sinervo and Svensson (2004: 172), "Goldschmidt's hopeful monster ... is in principle possible if mutations occur in regulative networks that buffer ontogenetic systems and yield functional integration; negative and positive regulation is common in endocrine systems and the organ systems targeted by hormones; one of the most famous natural examples of a hopeful monster, the axolotl, involves a loss-of-function mutation in an endocrine gene of major effect." Thus, "the likelihood of evolving hopeful monsters and morphological novelty is simplified if change is targeted to functionally integrated modules." Also, as recently noted by Dittrich-Reed and Fitzpatrick (2013: 311), growing "empirical and theoretical research on hybrid speciation have revived the hopeful monster in a new, more credible form." Namely, recombination of parental chromosomes in the F_2 and later generations during hybridization can generate genotypes that express phenotypes outside the normal range of variation observed in either parental gene pool, a phenomenon termed transgressive segregation." Transgressive hybrids often have higher fitness in novel environments, thus increasing the likelihood of divergence from parental populations. They list a few examples of new phenotypes that seemingly arose from hybridization: "extreme size of tiger $\times$ lion F_1 hybrids, unique shapes and colors of hybrid orchids, ability of recombinant sunflowers to thrive in extreme habits, specialization on a novel host plant in lonicera flies, and expression of novel gene transcripts (including new exons) via alternative splicing in hybrid poplars." As they recognized, "not all specific examples are relevant in nature, and not all would qualify as evolutionary novelty under certain definitions," but according to them such cases serve to illustrate "sudden appearance of profound differences between parents and hybrid offspring reminiscent of Goldschmidt's hopeful monsters."

Interestingly, the above discussion and the examples provided in this paper emphasize a profound link between Alberch's logic of "monsters" and Goldschmidt's hopeful "monsters": they are deeply related to, and dependent on, the highly constrained and linked developmental mechanisms mentioned in Waddington's notion of homeorhesis and Gerhart and Kirschner's concept of facilitated variation (see section Brief historical Introduction to Studies on Links between Evolution and Developmental Anomalies). That is, within this view it would not be so unexpected that Goldschmidt's ('40) hopeful "monsters" could occur, and eventually survive and in some cases potentially thrive, in evolution. For instance, at first sight it may seem very difficult to explain how a full extra appendage might appear with not only an internal skeleton but also soft tissues, skin, or tissues as it may in human congenital malformations (e.g., someone with three forelimbs). But taking into account Waddington's notion of home-

orhesis and Gerhart and Kirschner's notion of facilitated variation, it is not so difficult to explain these phenomena, because if a limb bud occurs in an abnormal position, it may still lead to the formation of an internal skeleton, which is developmentally associated with the formation of muscles that are in turn linked with the formation of nerves and blood vessels, and so on (see the ectopic hindlimb zeugopod and autopod in a chameleon embryo in Fig. 3C). This was precisely the point of Balon (2004), who is a strong proponent of the notion of saltatory evolution. However, it is also important to note that for some taxa that were previously seen as hopeful "monsters," such as turtles, the more fossils that are discovered, the more we know that the transitions toward the current forms was actually a gradual one (see, e.g., Kemp 2016). So, it is likely that at least in some cases what seems to be evidence of apparent saltational evolution is just due to a lack of an appropriate fossil record, although as explained in this paper, there are also many morphological changes that do seem to be the result of evolutionary saltations.

The above discussion and examples also reveal that opposing views of teratology such as Alberch's logic of "monsters" and Shapiro et al.'s ('83) "lack of homeostasis" model concern above all different levels of abnormal severity. Shapiro's model states that in, for example, trisomic individuals the presence of a whole extra functioning chromosome or of a large chromosome segment causes a *general* disruption of evolved genetic balance (for more details, see Diogo et al., 2015a). This model, therefore, refers mainly to cases that are so severe that not only Waddington's normal homeostasis but even homeorhesis are perpetually disrupted, the resulting phenotype being more unorganized/unpredictable than in Alberch's logic of "monsters." This is because Alberch refers to cases in which there is a disruption of normality, but the strong constrained mechanisms involved in homeorhesis can still lead to a "logic" (order) even within abnormality. This is the logic that can thus eventually lead to the existence of Goldschmidt's hopeful "monsters." In fact, Goldschmidt's notion of "phenocopies," that is, experimentally produced abnormalities that mimic certain mutants of untreated organisms (Gilbert, '88), is very similar to Alberch's logic of "monsters": induced defects are often seen in natural mutants as well as in variants of the normal population of other species or in the evolutionary changes that occurred in other taxa. It is hoped that the present paper will bring further discussion on these topics—ideally through the accumulation of more empirical data linking developmental, pathology, and morphological macroevolution—and bring more of our peers to the fascinating challenge of exploring the links between developmental anomalies and macroevolutionary changes.

ACKNOWLEDGEMENTS

Age ranges of taxa for Guinard's part are provided by fossilworks.org, as well as complementary measurements of specimens; silhouettes used for Fig. 2 are provided by phylopic.org (credits: Scott Hartman, Matt Martyniuk, T. Michael Keesey, Craig Dylke, Stephen O'Connor, Robert Gay, B.H. Michael, and Emily Willoughby). Diogo's part is partially funded by an NSF Bio Anth grant (ID number 1516557) and Howard University College of Medicine. Diaz's part was partially funded by La Sierra University's College of Arts and Science. We also want to thank the associate editor of *Journal of Experimental Zoology B* and two anonymous reviewers for their wise comments and suggestions, and to Gunter Wagner, in particular, for inviting us to be part of this special issue on "Developmental Evolution in Biomedical Research."

LITERATURE CITED

Adams DC, Nistri A. 2010. Ontogenetic convergence and evolution of foot morphology in European cave salamanders (Family: Plethodontidae). BMC Evol Biol 10:216.

Al-Qattan MM, Yang Y, Kozin SH. 2009. Embryology of the upper limb. J Hand Surg Am 34:1340–1350.

Alberch P, Gale EA. 1983. Size dependence during the development of the amphibian foot. Colchicine-induced digital loss and reduction. Development 76:177–197.

Alberch P, Gale EA. 1985. A developmental analysis of an evolutionary trend: digital reduction in amphibians. Evolution 39:8–23.

Alberch P. 1981. Convergence and parallelism in foot morphology in the neotropical salamander genus Bolitoglossa. Evolution 35:84–100.

Alberch P. 1989. The logic of monsters: Evidence for internal constraint in development and evolution. Geobios 22:21–57.

Ancet P. 2006. L'observation des monstres dans l'œuvre d'Etienne Geoffroy Saint-Hilaire. Cah Philos 108:23–38.

Balon EK. 2004. Alternative ontogenies and evolution: a farewell to gradualism. In: Hall BK, Pearson RD, Müller GB, editors. Environment, development and evolution: toward a synthesis (The Vienna series in theoretical biology). Massachussetts: A Bradford Book. p 37–66.

Bateson W. 1894. Materials for the study of variation treated with especial regard to discontinuity in the origin of species. London: Macmillan.

Beederman M, Farina EM, Reid RR. 2014. Molecular basis of cranial suture biology and disease: osteoblastic and osteoclastic perspectives. Genes Dis 1:120–125.

Bier E, McGinnis W. 2003. Model organisms in development and disease. In: Epstein CJ, Erikson RP, Wynshaw-Boris A, editors. Molecular basis of inborn errors of development. Oxford: Oxford University Press. p 25–45.

Bininda-Emonds ORP, Jeffery JE, Sánchez-Villagra MR, et al. 2007. Forelimb-hindlimb developmental timing changes across tetrapod phylogeny. BMC Evol Biol 7:1–7.

Bonaparte JF, Novas FE, Coria RA. 1990. *Carnotaurus sastrei* Bonaparte, the horned, lightly built carnosaur from the middle cretaceous of Patagonia. Contrib Sci Nat Hist Museum Los Angeles County 416:1–42.

Brochu CA. 2000. A digitally-rendered endocast for *Tyrannosaurus rex*. J Vertebr Paleontol 20:1–6.

Brochu CA. 2003. Osteology of *Tyrannosaurus rex*: insights from a nearly complete skeleton and high-resolution computed tomographic analysis of the skull. J Vertebr Paleontol 22:1–138.

Brusatte SL, Norell MA, Carr TD, et al. 2010. Tyrannosaur paleobiology: new research on ancient exemplar organisms. Science 329:1481–1485.

Brusatte SL, Benson RBJ, Norell MA. 2011. The anatomy of *Dryptosaurus aquilunguis* (Dinosauria: Theropoda) and a review of its tyrannosauroid affinities. Am Museum Novit 15:1–53.

Burtch RL. 1966. Nomencalture for congenital skeletal limb deficiencies, a revision of the Frantz and O'Rahilly classification. Artif Limbs 10:24–35.

Carroll SB, Weatherbee SD, Langeland JA. 1995. Homeotic genes and the regulation and evolution of insect wing number. Nature 375:58–61.

Carroll SB, Grenier JK, Weatherbee SD. 2004. From DNA to diversity: molecular genetics and the evolution of animal design. 2nd edition. New York: Blackwell Publishers.

Center for Disease Control and Prevention. 2016. Birth defects. Available online at: http://www.cdc.gov/ncbddd/birthdefects/ access date: 5 March 2016.

Cihak R. 1972. Ontogenesis of the skeleton and intrinsic muscles of the human hand and foot. Adv Anat Embryol Cell Biol 46:1–194.

Conte D, Garaffo G, Lo Iacono N, et al. 2016. The apical ectodermal ridge of the mouse model of ectrodactyly Dlx5;Dlx6$^{-/-}$ shows altered stratification and cell polarity, which are restored by exogenous Wnt5a ligand. Hum Mol Genet 25:740–754.

Day HJB. 1991. The ISO/ISPO classification of congenital limb deficiency. Prosth Ortho Int 15:67–69.

Depew MJ, Simpson CA. 2006. 21st century neontology and the comparative development of the vertebrate skull. Dev Dyn 235:1256–1291.

Diaz-Mendoza MJ, Lorda-Diez CI, Montero JA, Garcia-Porrero JA, Hurle JM. 2013. Interdigital cell death in the embryonic limb is associated with depletion of Reelin in the extracellular matrix. Cell Death Dis 4:e800.

Diaz RE, Trainor PA. 2015. Hand/foot splitting and the "re-evolution" of mesopodial skeletal elements during the evolution and radiation of chameleons. BMC Evol Biol 15:184.

Dimitrov BI, Voet T, De Smet L, Vermeesch JR, Devriendt K, Fryns JP, Debeer P. 2010. Genomic rearrangements of the *GREM1–FMN1* locus cause oligosyndactyly, radio-ulnar synostosis, hearing loss, renal defects syndrome and Cenani-Lenz-like non-syndromic oligosyndactyly. Journal of Medical Genetics 47:56974.

Diogo R. 2016. Where is the evo in evo-devo (evolutionary developmental biology)? J Exp Zool B Mol Dev Evol 326:9–18.

Diogo R, Molnar J. 2016. Links between evolution, development, human anatomy, pathology, and medicine, with a proposition of a redefined anatomical position and notes on constraints and morphological "imperfections". J Exp Zool B Mol Dev Evol 326:215–224.

Diogo R, Wood B. 2011. Soft-tissue anatomy of the primates: phylogenetic analyses based on the muscles of the head, neck, pectoral region and upper limb, with notes on the evolution of these muscles. J Anat 219:273–359.

Diogo R, Wood B. 2012a. Comparative anatomy and phylogeny of primate muscles and human evolution. Oxford: Taylor & Francis.

Diogo R, Wood B. 2012b. Violation of Dollo's Law: evidence of muscle reversions in primate phylogeny and their implications for the understanding of the ontogeny, evolution and anatomical variations of modern humans. Evolution 66:3267–3276.

Diogo R, Wood B. 2013. The broader evolutionary lessons to be learned from a comparative and phylogenetic analysis of primate muscle morphology. Biol Rev 88:988–1001.

Diogo R, Wood B. 2016. Origin, development and evolution of primate muscles, with notes on human anatomical variations and anomalies. In: Boughner J, Rolian C, editors. Developmental approaches to human evolution. Hoboken: John Wiley & Sons, Inc. p 167–204.

Diogo R, Esteve-Altava B, Smith C, Boughner JC, Rasskin-Gutman D. 2015a. Anatomical network comparison of human upper and lower, newborn and adult, and normal and abnormal limbs, with notes on development, pathology and limb serial homology vs homoplasy. PLoS One 10:e0140030.

Diogo R, Smith CM, Ziermann JM. 2015b. Evolutionary developmental pathology and anthropology: a new field linking development, comparative anatomy, human evolution, morphological variations and defects, and medicine. Dev Dyn 244:1357–1374.

Diogo R, Walsh S, Smith C, Ziermann JM, Abdala V. 2015c. Towards the resolution of a long-standing evolutionary question: muscle identity and attachments are mainly related to topological position and not to primordium or homeotic identity of digits. J Anat 226:523–529.

Diogo R, Noden D, Smith CM, et al. 2016. Learning and understanding human anatomy and pathology: an evolutionary and developmental guide for medical students. Oxford: Taylor & Francis.

Dittrich-Reed DR, Fitzpatrick BM. 2013. Transgressive hybrids as hopeful monsters. Evol Biol 40:310–315.

Duhamel B. 1972. L'œuvre tératologique d'Etienne Geoffroy Saint-Hilaire. Rev Hist Sci 25:337–346.

Duijf PHG, van Bokhoven H, Brunner HG. 2003. Pathogenesis of split-hand/split-foot malformation. Hum Mol Genet 12:R51–R60.

Epstein CJ, Erickson RP, Wynshaw-Boris W. 2008. Inborn errors of development (Oxford monographs on medical genetics). 2nd edition. Oxford: Oxford University Press.

Ermito S, Dinatale A, Carrara S, et al. 2009. Prenatal diagnosis of limb abnormalities: role of fetal ultrasonography. J Prenat Med 3: 18–22.

Esteve-Altava B, Rasskin-Gutman D. 2015. Evo-devo insights from pathological networks: exploring craniosynostosis as a developmental mechanism for modularity and complexity in the human skull. J Anthropol Sci 93:103–117.

Esteve-Altava B, Marugán-Lobón J, Botella H, Rasskin-Gutman D. 2013. Structural constraints in the evolution of the tetrapod skull

complexity: Williston's law revisited using network models. Evol Biol 40:209–219.
Esteve-Altava B, Diogo R, Smith C, Boughner JC, Rasskin-Gutman D. 2015. Anatomical networks reveal the musculoskeletal modularity of the human head. Sci Rep 5:8298.
Favier B, Rijli FM, Fromental-Ramain C, et al. 1996. Functional cooperation between the non-paralogous genes Hoxa-10 and Hoxd-11 in the developing forelimb and axial skeleton. Development 122:449–460.
Frantz CH, O'Rahilly R. 1961. Congenital Skeletal Limb Deficiencies. J Bone Joint Surg 43:1202–1224.
Galis F. 1999. Why do almost all mammals have seven cervical vertebrae? Developmental constraints, Hox genes, and cancer. J Exp Zool 285:19–26.
Gasser RF. 1967. The development of the facial muscles in man. Am J Anat 120:357–375.
Geoffroy Saint-Hilaire É. 1818–1822. Philosophie anatomique. Paris: Baillière.
Geoffroy Saint-Hilaire I. 1832–1837. Histoire générale et particulière des anomalies de l'organisation chez l'homme et les animaux. Paris: Baillière.
Gerhart J, Kirschner M. 2005. The plausibility of life: resolving Darwin's dilemma. Yale: Yale University Press.
Gerhart J, Kirschner M. 2007. The theory of facilitated variation. Proc Natl Acad Sci USA 104:8582–8589.
Gilbert SF. 1988. Cellular politics: just, Goldschmidt, and the attempts to reconcile embryology and genetics. In: Rainger R, Benson K, Malenschein J, editors. The American development of biology. Philadelphia: University of Pennsylvania Press. p 311–346.
Gilbert SF, Epel D. 2009. Ecological developmental biology: integrating medicine, epigenetics, and evolution. Sunderland, Massachusetts: Sinauer Associates.
Gold NB, Westgate M-N, Holmes LB. 2011. Anatomic and etiological classification of congenital limb deficiencies. Am J Med Genet A 155:1225–1235.
Goldschmidt R. 1940. The material basis of evolution. New Haven: Yale University Press.
Gould SJ. 1977. Ontogeny and phylogeny. Cambridge, MA: Belknap Press.
Gould SJ. 2002. The structure of evolutionary theory. Cambridge, MA: Belknap Press (Harvard).
Gregory WK. 1935. "Williston"s Law' relating to the evolution of skull bones in vertebrates. Am J Phys Anthropol 20:123–152.
Gross JB, Hanken J. 2008. Review of fate-mapping studies of osteogenic cranial neural crest in vertebrates. Dev Biol 317:389–400.
Guinard G. 2012. Evolutionary concepts meet the neck of penguins (Aves: Sphenisciformes), towards a "survival strategy" for evo-devo. Theory Biosci 131:231–242.
Guinard G. 2015. Introduction to evolutionary teratology, with the example of forelimbs of Tyrannosauridae and Carnotaurinae (Dinosauria: Theropoda). Evol Biol 42:20–41.
Guinard G. 2016. *Limusaurus inextricabilis* (Theropoda: Ceratosauria) gives a hand to evolutionary teratology: a complementary view on avian manual digits identities. Zool J Linn Soc 176:674–685.
Guinard G, Marchand D. 2010. Modularity and complete natural homeoses in cervical vertebrae of extant and extinct penguins (Aves: Sphenisciformes). Evol Biol 37:210–226.
Hall BK. 2001. Organic selection: proximate environmental effects on the evolution of morphology and behaviour. Biol Philos 16:215–237.
Hall BK. 2003a. Baldwin and beyond: organic selection and genetic assimilation. In: Weber BH, Depew DJ, editors. Evolution and learning: the baldwin effect reconsidered. Cambridge: MIT Press. p 141–167.
Hall BK. 2003b. Descent with modification: the unity underlying homology and homoplasy as seen through an analysis of development and evolution. Biol Rev Camb Philos Soc 78:409–433.
Hall BK, editor. 2007. Fins into limbs: evolution, development and transformation. Chicago: University of Chicago Press.
Hallgrimsson B, Percival CJ, Green R, et al. 2015. Morphometrics, 3D imaging, and craniofacial development. Curr Top Dev Biol 115:561–597.
Hanken J, Hall BK, editors. 1993a. The skull, volume 1: development. Chicago: University of Chicago Press.
Hanken J, Hall BK, editors. 1993b. The skull, volume 2: patterns of structural and systematic diversity. Chicago: University of Chicago Press.
Hanken J, Hall BK editors. 1993c. The Skull, Volume 3: Functional and Evolutionary Mechanisms. Chicago: University of Chicago Press.
Hennekam R, Allanson J, Krants I. 2010. Gorlin's syndromes of the head and neck (Oxford Monographs on medical genetics). 5th edition. Oxford: Oxford University Press.
Hernandez-Martinez R, Covarrubias L. 2011. Interdigital cell death function and regulation: new insights on an old programmed cell death model. Dev Growth Differ 53:245–258.
Hildebrand M, Bramble DM, Liem KF, Wake DB. 1985. Functional vertebrate morphology. Cambridge, Massachusetts: Belknap Press.
Hobbs CA, Cleves MA, Simmons CJ. 2002. Genetic epidemiology and congenital malformations—from the chromosome to the crib. Arch Pediatr Adolesc Med 156:315–320.
Huang C, Hales BF. 2009. Teratogen responsive signaling pathways in organogenesis stage mouse limbs. Reprod Toxicol 27:103–110.
Jaekel M, Wake DB. 2007. Developmental processes underlying the evolution of a derived foot morphology in salamanders. Proc Natl Acad Sci USA 104:20437–20442.
Kemp TS. 2016. The origin of higher taxa—paleobiological, developmental and ecological perspectives. Oxford: Oxford University Press.
Klembara J. 2001. Postparietal and prehatching ontogeny of the supraoccipital in *Alligator mississippiensis* (Archosauria, Crocodylia). J Morphol 249:147–153.
Knoll AH, Carroll SB. 1999. Early animal evolution: emerging views from comparative biology and geology. Science 284:2129–2137.

Koyabu D, Son NT. 2014. Patterns of postcranial ossification and sequence heterochrony in bats: life histories and developmental trade-offs. J Exp Zool B Mol Dev Evol 322:607–618.

Koyabu D, Maier W, Sánchez-Villagra MR. 2012. Paleontological and developmental evidence resolve the homology and dual embryonic origin of a mammalian skull bone, the interparietal. Proc Natl Acad Sci USA 109:14075–14080.

Koyabu D, Werneburg I, Morimoto N, et al. 2014. Mammalian skull heterochrony reveals modular evolution and a link between cranial development and brain size. Nat Commun 5.

Larsson HCE, Heppleston AC, Elsey RM. 2010. Pentadactyl ground state of the manus of Alligator mississippiensis and insights into the evolution of digital reduction in Archosauria. J Exp Zool B Mol Dev Evol 314B:571–579.

Le Guyader H. 2004. Étienne Geoffroy Saint-Hilaire. A Visionary Naturalist. Chicago: University of Chicago Press. 1772–1844.

Leroi AM. 2014. The lagoon: how Aristotle invented science. London: Bloomsbury.

Levin DA. 2002. The role of chromosomal change in plant evolution. New York: Oxford University Press.

Levinton JS. 2001. Genetics, paleontology and macroevolution. New York: Cambridge University Press.

Lupton C, Burd L, Harwood R. 2004. Cost of fetal alcohol spectrum disorders. Am J Med Genet C Semin Med Genet 127C:42–50.

Lyons K, Ezaki M. 2009. Molecular regulation of limb growth. J Bone Joint Surg 91:47–52.

Maleev EA. 1974. Gigantic carnosaurs of the family Tyrannosauridae. Joint Sov Paleontol Exped Trans 1:132–191.

Malik S. 2012. Syndactyly: phenotypes, genetics and current classification. Eur J Hum Genet 20:817–824.

Mallarino R, Abzhanov A. 2012. Paths less traveled: evo-devo approaches to investigating animal morphological evolution. Annu Rev Cell Dev Biol 28:743–763.

Minelli A. 2003. The development of animal form: ontogeny, morphology, and evolution. New York: Cambridge University Press.

Minelli A. 2009. Forms of becoming—the evolutionary biology of development. Princeton: Princeton University Press.

Minoux M, Rijli FM. 2010. Molecular mechanisms of cranial neural crest cell migration and patterning in craniofacial development. Development 137:2605–2621.

Moeller C, Swindell EC, Kispert A, Eichele G. 2003. Carboxypeptidase Z (CPZ) modulates Wnt signaling and regulates the development of skeletal elements in the chicken. Development 130:5103–5111.

Muenke M, Kress W, Collmann H, Solomon BD, Schmid M editors. 2011. Craniosynostoses: molecular genetics, principles of diagnosis, treatment (monographs in human genetics, vol. 19). Basel: S. Karger Publishers.

Müri RM. 2016. Cortical control of facial expression. J Comp Neurol 524:1578–1585.

Niederreither K, Vermot J, Schuhbaur B, Chambon P, Dollé P. 2002. Embryonic retinoic acid synthesis is required for forelimb growth and anteroposterior patterning in the mouse. Development 129:3563–3574.

Olson ME. 2012. The developmental renaissance in adaptationism. Trends Ecol Evol 27:278–287.

Opitz JM, Reynolds JF. 1985. The developmental field concept. Am J Med Genet 21:1–11.

Osborn HF. 1905. Tyrannosaurus and other Cretaceous carnivorous dinosaurs. Am Museum Nat Hist Bull 21:259–265.

Panchen AL. 2001. Étienne Geoffroy St.-Hilaire: father of "evo-devo"? Evol Dev 3:41–46.

Pantalacci S, Semon M. 2015. Transcriptomics of developing embryos and organs: a raising tool for evo-devo. J Exp Zool B Mol Dev Evol 324:363–371.

Peter I, Davidson E. 2015. Genomic control process: development and evolution. New York: Academic Press.

Peter IS, Davidson EH. 2011. Evolution of gene regulatory networks that control embryonic development of the body plan. Cell 144:970–985.

Pigliucci M, Müller GB. 2010. Evolution—the extended synthesis. Cambridge: MIT Press.

Pinero J, Queralt-Rosinach N, Bravo A, et al. 2015. DisGeNET: a discovery platform for the dynamical exploration of human diseases and their genes. Database (Oxford) 2015:bav028.

Pires-daSilva A, Sommer RJ. 2003. The evolution of signalling pathways in animal development. Nat Rev Genet 4:39–49.

Pol D, Rauhut OWM. 2012. A Middle Jurassic abelisaurid from Patagonia and the early diversification of theropod dinosaurs. Proc R Soc London B Biol Sci 279:3170–3175.

Pratihar S, Nath RP, Kundu JK. 2010. Hox genes and its role in animal development. Int J Sci Nat 1:101–103.

Proudfoot A, Axelrod HL, Geralt M, et al. 2016. Dlx5 homeodomain:DNA complex: structure, binding and effect of mutations related to split hand and foot malformation syndrome. J Mol Biol 428:1130–1141.

Raff RA. 1996. The shape of life: genes, development, and the evolution of animal form. Chicago: University of Chicago Press.

Reiter LT, Potocki L, Chien S, Gribskov M, Bier E. 2001. A systematic analysis of human disease-associated gene sequences in Drosophila melanogaster. Genome Res 11:1114–1125.

Rice DP, Sharpe PT, editors. 2008. Craniofacial sutures: development, disease and treatment (frontiers of oral biology, vol. 12). Basel: S. Karger Publishers.

Richards RJ. 1992. The meaning of evolution: the morphological construction and ideological reconstruction of Darwin's theory. Chicago: University of Chicago Press.

Richards RJ. 2002. The romantic conception of life: science and philosophy in the age of Goethe. Chicago: University of Chicago Press.

Richards RJ. 2008. The tragic sense of life: Ernst Haeckel and the struggle over evolutionary thought. Chicago: University of Chicago Press.

Richardson MK, Gobes SMH, Van Leeuwen AC, et al. 2009. Heterochrony in limb evolution: developmental mechanisms and natural selection. J Exp Zool B 312:639–664.

Richtsmeier JT, Flaherty K. 2013. Hand in glove: brain and skull in development and dysmorphogenesis. Acta Neuropathol 125:469–489.

Richtsmeier JT, Aldridge K, DeLeon VB, et al. 2006. Phenotypic integration of neurocranium and brain. J Exp Zool B Mol Dev Evol 306:360–378.

Rostand J. 1964. Etienne Geoffroy Saint-Hilaire et la tératogénèse expérimentale. Rev Hist Sci 17:41–50.

Russell DA. 1970. Tyrannosaurs from the Late Cretaceous of western Canada. Natl Mus Nat Sci Publ Paleontol 1:1–34.

Sagai T, Hosoya M, Mizushina Y, Tamura M, Shiroishi T. 2005. Elimination of a long-range cis-regulatory module causes complete loss of limb-specific Shh expression and truncation of the mouse limb. Development 132:797–803.

Salinas-Saavedra M, Gonzalez-Cabrera C, Ossa-Fuentes L, et al. 2014. New developmental evidence supports a homeotic frameshift of digit identity in the evolution of the bird wing. Front Zool 11: 1–10.

Santagati F, Rijli FM. 2003. Cranial neural crest and the building of the vertebrate head. Nat Rev Neurosci 4:806–818.

Schlichting CD, Pigliucci M. 1998. Phenotypic evolution: a reaction norm perspective. Sunderland: Sinauer Associates.

Schneider RA, Hu D, Helms JA. 1999. From head to toe: conservation of molecular signals regulating limb and craniofacial morphogenesis. Cell Tissue Res 296:103–109.

Schwabe GC, Mundlos S. 2004. Genetics of congenital hand anomalies. Handchir Mikrochir Plast Chir 36:85–97.

Schwenk K. 2000. Feeding: form, function and evolution in tetrapod vertebrates. New York: Academic Press.

Senter P, Moch JG. 2015. A critical survey of vestigial structures in the postcranial skeletons of extant mammals. Peer J 3: e1439.

Shapiro BL, Hermann J, Opitz JM. 1983. Down syndrome—a disruption of homeostasis. Am J Med Genet 14:241–269.

Shubin N, Tabin C, Carroll S. 1997. Fossils, genes and the evolution of animal limbs. Nature 388:639–648.

Shum L, Coleman CM, Hatakeyama Y, Tuan RS. 2003. Morphogenesis and dysmorphogenesis of the appendicular skeleton. Birth Defects Res C Embryo Today Rev 69:102–122.

Sidor CA. 2001. Simplification as a trend in synapsid cranial evolution. Evolution 55:1419–1442.

Siegenthaler JA, Pleasure SJ. 2011. We have got you "covered": how the meninges control brain development. Curr Opin Genet Dev 21:249–255.

Sinervo B, Svensson EI. 2004. The origin of novel phenotypes: correlational selection, epistasis, and speciation. In: Hall BK, Pearson RD, Müller GB, editors. Environment, development and evolution: toward a synthesis (The Vienna series in theoretical biology). Massachusetts: A Bradford Book. p 171–194.

Smith CM, Molnar JL, Ziermann JM, et al. 2015. Muscular and skeletal anomalies in human trisomy in an evo-devo context: description of a T18 cyclopic fetus and comparison between Edwards (T18), Patau (T13) and Down (T21) syndromes using 3-D imaging and anatomical illustrations. Oxford: Taylor & Francis.

Stevenson RE, Hall JG editors. 2016. Human malformations and related anomalies (Oxford monographs on medical genetics). 3rd edition. Oxford: Oxford University Press.

Trainor PA. 2010. Craniofacial birth defects: the role of neural crest cells in the etiology and pathogenesis of Treacher Collins syndrome and the potential for prevention. Am J Med Genet A 152A:2984–2994.

Tubbs RS, Malefant J, Loukas M, et al. 2016. Enigmatic human tails: a review of their history, embryology, classification, and clinical manifestations. Clin Anat 29:430–438.

Vargas AO, Fallon JF. 2005. The digits of the wing of birds are 1, 2, and 3. A review. J Exp Zool B Mol Dev Evol 304B:206–219.

Vargas AO, Wagner GP. 2009. Frame-shifts of digit identity in bird evolution and cyclopamine-treated wings. Evol Dev 11: 163–169.

Verhulst J. 2003. Developmental dynamics in humans and other primates: discovering evolutionary principles through comparative morphology. Ghent: Adonis.

Vogt TF, Duboule D. 1999. Antagonists go out on a limb. Cell 99:563–566.

Waddington CH. 1942. Canalization of development and the inheritance of acquired characters. Nature 150:563–565.

Waddington CH. 1952a. Selection of the genetic basis for an acquired character. Nature 169:278.

Waddington CH. 1952b. Selection of the genetic basis for an acquired character: reply to Begg. Nature 169:625–626.

Waddington CH. 1953a. The "Baldwin effect," "genetic assimilation" and "homeostasis". Evolution 7:386–387.

Waddington CH. 1953b. Epigenetics and evolution. Symp Soc Exp Biol 7:186–199.

Waddington CH. 1953c. The evolution of adaptations. Endeavour 12:134–139.

Waddington CH. 1953d. Genetic assimilation of an acquired character. Evolution 7:118–126.

Waddington CH. 1956. Genetic assimilation of the bithorix phenotype. Evolution 10:1–13.

Waddington CH. 1957. The strategy of the genes. London: George Allen & Unwin Ltd.

Waddington CH. 1961a. Genetic assimilation. Adv Genet 10:257–290.

Waddington CH. 1961b. The nature of life. New York: Harper & Row.

Waddington CH. 1975. The evolution of an evolutionist. Ithaca: Cornell University Press.

Wagner GP, Gauthier JA. 1999. 1,2,3 = 2,3,4: a solution to the problem of the homology of the digits in the avian hand. Proc Natl Acad Sci USA 96:5111–5116.

Wagner GP, Schwenk K. 2000. Evolutionarily stable configurations: functional integration and the evolution of phenotypic stability. In: Hecht MK, MacIntyre RJ, Clegg MT, editors. Evolutionary biology, vol. 31. New York: Kluwer Academic/Plenum Press. p 155–217.

Wang Z, Young RL, Xue H, Wagner GP. 2011. Transcriptomic analysis of avian digits reveals conserved and derived digit identities in birds. Nature 477:583–586.

Weatherbee SD, Behringer RR, Rasweiler JJ 4th, Niswander LA. 2006. Interdigital webbing retention in bat wings illustrates genetic changes underlying amniote limb diversification. Proc Natl Acad Sci USA 103:15103–15107.

Weidersheim R. 1895. The structure of man—an index to his past history. London: MacMillan & Co.

Weisbecker V, Nilsson M. 2008. Integration, heterochrony, and adaptation in pedal digits of syndactylous marsupials. BMC Evol Biol 8:1–14.

West-Eberhard MJ. 2003. Developmental plasticity and evolution. Oxford: Oxford University Press.

World Health Organization. 2015. Congenital anomalies. Available online at: http://www.who.int/mediacentre/factsheets/fs370/en/ access date: 5 April 2016.

Xu X, Clark JM, Forster CA, et al. 2006. A basal tyrannosauroid dinosaur from the Late Jurassic of China. Nature 439:715–718.

Xu X, Clark JM, Mo J, et al. 2009. A Jurassic ceratosaur from China helps clarify avian digital homologies. Nature 459:940–944.

Xu X, Norell MA, Kuang X, et al. 2004. Basal tyrannosauroids from China and evidence for protofeathers in tyrannosauroids. Nature 431:680–684.

Yang Y, Kozin SH. 2009. Cell signaling regulation of vertebrate limb growth and patterning. J Bone Joint Surg 91:76–80.

Young NM, Wagner GP, Hallgrímsson B. 2010. Development and the evolvability of human limbs. Proc Natl Acad Sci USA 107:3400–3405.

Zakany J, Duboule D. 2007. The role of Hox genes during vertebrate limb development. Curr Opin Genet Dev 17:359–366.

Zákány J, Fromental-Ramain C, Warot X, Duboule D. 1997. Regulation of number and size of digits by posterior Hox genes: a dose-dependent mechanism with potential evolutionary implications. Proc Natl Acad Sci USA 94:13695–13700.

Zeller R, Lopez-Rios J, Zuniga A. 2009. Vertebrate limb bud development: moving towards integrative analysis of organogenesis. Nat Rev Genet 10:845–858.

Zhao H, Feng J, Ho T-V, et al. 2015. The suture provides a niche for mesenchymal stem cells of craniofacial bones. Nat Cell Biol 17:386–396.

Zou H, Niswander L. 1996. Requirement for BMP signaling in interdigital apoptosis and scale formation. Science 272:738–741.

Zuniga A, Zeller R, Probst S. 2012. The molecular basis of human congenital limb malformations. Wiley Interdiscip Rev Dev Biol 1:803–822.

Zuzarte-Luis V, Hurle JM. 2005. Programmed cell death in the embryonic vertebrate limb. Semin Cell Dev Biol 16:261–269.