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REVIEW

How Do Complex Phenotypes Evolve? Solving the "Gene for X" Problem with Atavisms, Homeosis and other Evo-Devo Surprises

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Abstract:

Helping students learn how major phenotypic shifts evolve is a major hurdle for biology educators. Pedagogical research shows how teachers can exploit the oft-misunderstood "gene for X" concept to explain how evolution, and complex phenotypes, often involve single changes to regulatory genes governing expression of structural genes during development. Such changes show that one mutation can make a big difference. Student surveys and feedback from general zoology, evolution, and anatomy/physiology courses confirm that evo-devo explanations help students relate microevolution to macroevolution, a frequent hang-up for evolution deniers. Although complex traits such as intelligence do not derive from a single gene, minor tweaks in gene regulators produce atavisms (sudden appearance of "throwback" features), homeotic mutants (whose altered features stem from shifts in developmental timing and location), and other major changes in organismal morphology. Biology educators must explain how evo-devo mechanisms profoundly shift the course of evolution and drive phenotypic change. Adult forms do not evolve into other forms, but their underlying development, which generates adult form, readily evolves. Pedagogical research results clearly demonstrate the utility of this focus.

Keywords: Evo-devo, Atavism, Homeosis, Development, Phenotype, Plasticity

Introduction: What is the "Gene for X" Concept?

The popular idea of a "gene for X"—that each biological trait owes its existence to the simple inheritance and expression of a corresponding single gene—is widely known and a frequent scourge of science educators. The basic concept predates the origin of the term "gene" itself (Portin and Wilkins, 2017). It traces its ancestry to Mendel's seminal work on the inheritance of discrete, particulate units in pea plants, and the correspondence of those units to familiar and readily observable physical characteristics of garden pea plants, Pisum sativum: flower color and position, seed color and texture, etc. Indeed, the ultimate dissemination and perpetuation of the "gene for X" concept largely derives from Mendel's success linking pea traits with inherited units, and the eventual promulgation of Mendel's straightforward explanation of the underlying mechanisms of dominance, segregation, and independent assortment. In short, Mendel's simple elucidation worked too well, aided by his choice of research subject (the garden pea displays simple monogenic traits, unlike other plants) along with the natural desire, on the part of both Mendel and his audience, for a simple, all-encompassing explanation.

The problem is that while the basic "gene for X" concept aptly describes the inheritance of numerous (but not all) traits for peas, and also of a few odd traits in human beings (e.g., widow's peak, hitchhiker's thumb, Hapsburg lip), the concept is—simplicity, memorability, and intuitive nature aside—a poor match for most human traits, particularly those that attract frequent scrutiny. There are some important human conditions, such as color blindness, blood type, and Huntington's disease, which are encoded by inheritance of a single allele. Unfortunately, there are far more key human traits, such as intelligence, introversion, and athletic coordination, not to mention human height, skin color, and eye/hair color, that attract much attention but are polygenic (encoded by multiple genes). The "gene for X" concept has led to contentious debates about possibilities of a "gene for" homosexuality, thrill-seeking, or other controversial issues (O'Riordan, 2012). Human (as opposed to pea) genetics, with its abundance of complex, polygenic traits that are heavily influenced not only by genotype but by epigenetic, epistatic, and environmental interaction, has led many educators to recommend new approaches in presenting basic biology to students, even at the lowest educational levels (Dougherty, 2010).

Such a transformation or at least renovation of genetics education is undoubtedly warranted (Dougherty, 2009). However, it must be recognized that the enduring impact of the unfortunately ubiquitous "gene for X" concept on biology students extends far beyond the subject of genetics. In particular, this calamitous cliché has major implications for students' understanding of evolution, chiefly in terms of what evolution entails and how it occurs (i.e., by what processes). This paper lays out the problem, as manifested in misconceptions of typical college biology students, and suggests specific topics and questions to address concerns posed by the "gene for X" problem and thereby to improve students' understanding of evolution.

Although the term polymorphism (literally, "many forms") typically refers to multiple gene variants and the corresponding diversity of phenotypes these alleles produce, polymorphism can also refer, in a broader sense, to phenotypic diversity within a population, species, or larger group, including all animals. It includes a multitude of diverse species plus their extraordinarily diverse morphology, physiology, and behavior. Where does all this diversity come from? How does it

arise? Explaining biodiversity based on countless single gene mutations is, for most students, a bridge too far: unsatisfying nonsense, easy to spout back to instructors, but much harder to take seriously or accept. Many students struggle mightily to link large-scale evolution to repeated gene mutations.

Ironically, the longstanding and intuitive "gene for X" concept can help students better understand genetic mechanisms of organismal change, especially as students learn the key difference between structural and regulatory genes and their implications for evolutionary-developmental biology, AKA "evo-devo" (Hiatt et al., 2013; Kampourakis and Minelli, 2014). One can capitalize on fascinating and alluring examples.

The author's pedagogical research findings suggest a need for clear concision to ensure that students assimilate key concepts along with memorable examples. Questionnaires and surveys of student views concerning evolution (theory and processes) reveal many lingering myths and misconceptions (Werth, 2009, 2012, 2013). Additionally, these studies clearly demonstrate the need to address such misconceptions head-on (Werth, 2009; Scharmann and Grauer, 2020; Tolman et al., 2021), not only by presenting more nuanced yet factual material, but especially by framing questions to prime student mindsets to accept surprising or counterintuitive perspectives.

Why is the "Gene for X" Concept Problematic for Evolution Education?

Part of the problem, paradoxically, lies in the explanatory success of basic Mendelian models in elucidating the inheritance of simple traits. Unfortunately, these straightforward explanations of general inheritance are so simple, sensible, and non-controversial that they often lead, unwittingly, to the conclusion that major phylogenetic change—e.g., from microbes to fish to humans—occurs via gradual accretion of stepwise modifications, even as, for many students, this beggars belief (Dougherty, 2009). As documented by anonymous surveys of introductory college biology students (Werth, 2009, 2012, 2013), three widespread and frequent complaints are:

1) "It's impossible for all of the world's biodiversity to have arisen by slow, steady accumulation of random mutations." Even over billions of years, this process is, to many minds, grossly implausible. Setting aside ubiquitous opposition to what is perceived to be an impossibly blind, mindless process, a related criticism is that:
2) "Organisms are far too complex to have arisen by a random process." Organs like hearts and eyeballs are irreducibly complex: they could not result from stepwise accumulation of small changes, because they are useless until fully formed. Half an eye is worthless.
3) Likewise, the molecular machinery of cells is seen as irreducibly intricate: "Something like blood clotting or hormonal function are much too complex to have evolved." These systems, critics argue, could never come from an occasional drumbeat of piecemeal mutations.

Even before Eldredge and Gould (1972) proposed their hypothesis of punctuated equilibrium (largely based on the fossil record), resistance to Darwin's original idea of slow, steady phyletic gradualism had appeared, both from field naturalism and paleontology, but also from molecular biology's burgeoning

findings in the 1940s and 1950s following evolution's modern synthesis. Complex transformations in biological form and function no longer needed to be explained by gradual, sequential nucleotide substitutions. Elucidation of transcription factors, promoter sequences, operons, and suppressor genes led to improved understanding of how small genetic changes can produce huge transformations in biological form and function, from the cellular and subcellular levels to whole organisms. Over the past two decades, results of the Human Genome Project, and simultaneous sequencing of the genomes of many other species, led us to appreciate how vast differences between species can be produced by changes in a surprisingly small number of genes via variable gene splicing and related mechanisms.

Just as we now recognize that complex traits are typically polygenic (controlled by multiple genes), we likewise now realize that organismal complexity reflects a deep homology (Held, 2017), wherein growth and differentiation of body parts such as limbs or eyes are governed by deeply inscribed and conserved molecular and embryological processes that apply to numerous distantly related taxa, including arthropods, molluscs, and vertebrates. We have learned from evo-devo that basic patterns of embryonic development are governed by gene toolkits, and that minor tweaks in regulatory genes can produce profound consequences (Hiatt et al., 2013; Kampourakis and Minelli, 2014; Losos, 2018; Diaz, 2020).

In short, whereas natural philosophers once espoused a motto of Natura non facit saltus ("nature does not make leaps"), today we understand that evolution frequently progresses by saltation rather than invariably by ultra-slow Darwinian gradualism. These bounding hops can arise by sudden environmental changes (Weiner, 1994) but just as often occur due to sudden mutations. This information must be presented to students. If they see how abrupt changes in toolkit genes produce major structural and functional leaps, they will correspondingly have a better grasp of evolutionary mechanisms. The following sections focus on relevant examples of such changes, with suggestions for how students can gain and apply richer understanding. Specifically, lessons on atavisms, homeosis, and related evo-devo mechanisms have shown tremendous utility in helping student learning (Werth, 2013).

Atavistic reversion

In biology, an atavism (from the Latin *atavus* for ancestor, or literally "great-great-great grandfather") is a reversion or throwback: reappearance of a formerly lost trait. The surprising presence of legs in whales or snakes, or a tail in humans, all involve the unexpected recurrence of a phenotypic feature that was present in ancestors, subsequently vanished, and later returned again. As Gould explained in his book *Hen's Teeth and Horse's Toes* (1983), what evolution has lost, development can quickly restore. Unlike the earliest birds, no living birds (Neornithes) possess teeth; all have a beak instead. Hence the tongue-in-cheek expression "rare as a hen's tooth" slyly refers to something so "rare" it is never found. Yet somewhat amazingly, chick embryos *can* be manipulated in the lab such that they are born with teeth.

How is this possible? Very simply, mutations in regulatory genes can suddenly "switch off" gene expression, meaning that a phenotypic feature is immediately silenced. At the same time, the underlying structural genes that code for the

feature—the avian teeth, cetacean hindlimbs, or human tail—remain present, just unexpressed, and they can later be switched back "on" by another chance mutation. The sudden reappearance of dormant evolutionary remnants reveals the dynamic interplay between ontogeny and phylogeny (Gould, 1977), and thus the key influence of toolkit genes.

In another example, Gould (1983) wrote of Julius Caesar's fabled "three-toed horse," which was not faster or stronger than other horses but simply notable for its extraordinary rarity. We know from the fossil record that the earliest ancestral horses possessed 3-4 toes on each limb. Modern horses retain only the middle (third) digit as the hoof, but an occasional and exceptional atavistic mutation allows other "missing" digits to appear, confirming that equine digit loss occurred not via loss of the genes coding for toes, but instead via spontaneous deactivation of their expression. Such deactivation was probably strongly selected for, in that excess structures (in this case, toes) were unnecessary and costly to produce. For an animal whose success depends on running quickly, having stripped-down limbs that are lighter and easier to move would be strongly selected for. It would mean the difference between surviving or not.

Recent research suggests that atavisms may be more common and important than imagined. According to the serial atavism model (Lineweaver et al., 2021), cancer occurs mainly by normal cells' reversion to ancestral types of cells, whose latent capabilities lie dormant, waiting to be unleashed to trigger uncontrolled cell growth. This also highlights the key point that phenotype involves far more than physical form. Just as vestiges can involve physiological or biochemical processes or behaviors, such as dogs walking in circles before setting down to rest (Werth, 2014), atavisms simply involve reappearance of former traits, but not necessarily structures.

Atavistic reversions reveal the extraordinary way in which one mutation can make a big difference. They demonstrate the profound power of developmental plasticity and the importance of evo-devo interaction. Once offered as embarrassing refutations of evolutionary change (Hall, 1995)—*Why would evolution lose something only to regain it later? And doesn't this debunk the notion that evolution operates by chance, and never goes down the same road twice?*—atavisms are now seen as constituting some of the strongest evidence for evolution.

Clearly, atavisms illuminate some of the major mysteries (and criticisms) of evolution:

- *How can species change relatively quickly?*
- *How can a tiny mutation lead to a major structural change?*
- *Why don't we always find intermediate forms in the fossil record?*
- *How can a lost feature return? Why does evolution occasionally lead to sudden U-turns?*
- *Why are some structural patterns (e.g., limbless vertebrates) common?*
- *How can developmental instructions persist even after features are lost?*

Atavisms readily address these and many other important (and frequent student) questions. Just as the fossil record of whale evolution has become, in recent decades, one of the best, and best-known, lines of evidence supporting evolution (Werth, 2020), so too the occasional surprise reappearance of cetacean legs also provides solid backing for evolutionary theory. The widely documented recent case of stubby but prominent hindlimbs in a captive bottlenose dolphin,

Tursiops truncatus, at an aquarium in Taiji, Japan (Ohsumi and Kato, 2008) provides abundant fodder for student discussion. What happened to the original legs of long-ago whale ancestors? Where did they go? How were they lost? Why were they not retained? What happens in rare cases when rudimentary, atavistic legs return? How is this possible? Why is this not more or less common? How does this compare to cases of newborn human babies with rudimentary tails?

Homeotic transformation

Another equally surprising and powerful evo-devo mechanism similar to atavism is homeosis, in which single mutations in crucial regulatory toolkit genes once again can yield major changes in organismal structure. These genes, dubbed homeotic genes, govern the precise placement and timing of developmental events. Homeotic mutations produce startling changes, such as serially homologous structures appearing in different (ectopic) places. A classic example is *antennapedia*, in which displaced legs of flies appear where antennae normally reside: on the head! Similar mutations unexpectedly displace wings or other structures. These are examples of heterotopy (literally, "different place"), a concept introduced by Ernst Haeckel (1866) to refer to evolutionary changes that alter spatial orientation, such as along bodily axes or germ layers, during organismal development. These axes and layers typically control body segmentation and overall patterning. Homeosis, and other heterotopic mutants in general, are known from a wide diversity of groups, including angiosperm and non-flowering plants and vertebrate and invertebrate animals.

Heterotopy is less well known than heterochrony, another evo-devo process involving fundamental and far-reaching evolved changes during development. Heterochrony (literally, "different timing") refers to changes that affect the timing rather than location of a structure's appearance. As with heterotopy, heterochrony occurs via homeotic mutations altering preprogrammed scheduling of crucial embryonic events. Heterochrony often leads to paedomorphosis, the appearance of juvenile traits in sexually mature adults. This occurs either via neoteny (retention of juvenile features) or progenesis (accelerated sexual maturity). Importantly, both heterotopy and heterochrony involve rewiring of a species' genome, leading to potentially rapid evolutionary change via subtly or profoundly altered development.

As with atavisms, homeotic mutants demonstrate that profound structural transformations occur with tiny tweaks to a "gene for X," albeit regulatory genes controlling the expression of structural genes rather than (as usually imagined) genes encoding and expressing structures themselves. In homeosis, gene regulators that shape organismal development by governing downstream gene networks are called homeotic genes. Like typical gene regulators, homeotic genes often encode transcription factors that in turn inhibit or activate control regions governing the expression of various structural genes.

The best-known and probably most common homeotic genes are called *Hox* genes, each of which includes a long (roughly 180 base pair) DNA sequence called a homeobox. Homeoboxes and Hox genes are strikingly conservative and demonstrate deep homology. Many Hox genes of Drosophila fruit flies are homologous to those of humans and other species. This strongly suggests that basic patterns of animal (and plant) development are ancient and longstanding, such that even highly disparate multicellular organisms share fundamental

underlying developmental mechanisms. Heterotopic and heterochronic transformations have been found to underlie major shifts in body plans of worms, echinoderms, chordates, and other animals, creating new kinds of embryos, which is how Haeckel (1866) discovered them. This shows how evolution can, with a few minor tweaks, shape bodies and generate endless new forms.

Biologists today generally use the term disparity to describe morphological differences within and between diverse species; they reserve the term diversity to denote the array of numerous different species themselves. Even within a single organism, such as a crayfish, there can be much disparity of, for example, jointed appendages: antennules, antennae, mandibles, maxillae, maxillipeds, chelipeds (claws), walking legs, swimmerets, pleopods, uropods, telsons, and so on. This disparity can, and likely did, arise from simple homeotic mutations in genes controlling heterotopy and heterochrony, producing numerous appendages with different structures and functions yet with shared serial homology. A familiar refrain: small mutations can generate big differences in organismal form.

This idea—that minor genotypic changes often yield major phenotypic change—was espoused by Richard Goldschmidt, whose 1940 book *The Material Basis of Evolution* introduced the term "hopeful monsters." Goldschmidt explained that hopeful monsters are organisms with novel body forms that could significantly shift evolution's course by proving adaptive (i.e., showing utility), with their genes inherited and better represented in succeeding generations (Diaz, 2020; Diogo, 2020). In this way, Goldschmidt bolstered the claim that biodiversity stems not only from an accumulation of small adaptive changes within a species (what is commonly referred to as microevolution). Evolution often proceeds instead via major transformations, including saltatory leaps and the appearance of entirely new forms (macroevolution) that depend on "macromutations."

This relates directly to a chief complaint of evolution's critics, doubters, and deniers:

- *How can trifling microevolution possibly lead to intense macroevolution?*

Many students admit that adaptive changes in giraffe stature and moth pigmentation make perfect sense, but leave much (if not everything) to be desired in that they fail to address how giraffes and moths arose in the first place from a primordial soup of unicellular prokaryotes. How does one explain the appearance of new species, not to mention higher-order taxonomic groups such as new phyla or classes? "*I understand how climate change could make polar bear fur coats thinner or thicker, but that doesn't explain how bears arose in the first place...*"

Biology educators typically attempt to link micro- and macroevolution simply by explaining that given sufficient time, many trivial changes eventually add up to big change. Frankly, this handwaving is unreasonable, counterintuitive, and intellectually unsatisfying for most people, including many students. Instead of directly addressing or even mildly mollifying this criticism, the purported eventual loose link between adaptive microevolution and transformative macroevolution appears to disengage many students, turning them off and shifting them into "OK, I'll repeat this on the exam so that I'll pass, but I'm still not buying it" mode.

The brilliance of evo-devo is that it effectively and easily explains precisely how slight, single mutations to DNA can generate huge biological changes. It exploits the comfortable and familiar (if generally misleading) "gene for X" trope to show how all the disparity within and between countless organismal forms,

extant and extinct, could arise by simple, straightforward, and indeed predictable ways.

Exaptation, apoptosis, induction, & evo-devo concepts linking mutation to macroevolution

Numerous other common misconceptions about or problems with evolution can be addressed with basic evo-devo concepts. For example, exaptation (AKA preadaptation) describes a process by which an existing trait serves a particular adaptive function, and then is co-opted to serve a partially or wholly different future function. Depending on one's outlook, and verb tense, this can also involve explaining a current trait in terms of a former (pre-existing) trait.

The classic example of exaptation involves feathers, which chiefly serve as locomotor structures to generate lift and thrust for flight, but which in fact simultaneously serve multiple additional functions in birds, including thermoregulation (as insulation to conserve body heat), communicative signaling and display for mating or other reasons, cryptic coloration and patterning, waterproofing and streamlining, and so on. Any one (or more) of these roles, or perhaps another entirely different role, such as creating a net-like structure to trap insects, might conceivably have preceded feathers' role in enabling flight. Other examples of exaptation include transformation of reptilian jaw bones to become the amplifying malleus and incus (tiny middle ear ossicles) for hearing in mammals, and the exaptive repurposing of lungs in basal fishes into air-filled, buoyancy-regulating swim bladders in non-air breathing fishes. As Gould explained (1980), a simple wrist bone of giant pandas, the radial sesamoid, became an exapted "thumb" analogue used to snag bamboo shoots.

Darwin appreciated the significance of preadaptation in explaining correlated shifts in organismal structure and function, as well as showing that species are imperfectly rather than optimally designed—they are cobbled from existing parts rather than designed de novo. Unfortunately, this concept is difficult for many people to embrace because of the all-encompassing dictum that "evolution works only in the here and now"; it cannot look ahead. This is why Gould and Vrba (1982) coined the term exaptation to replace the problematic term preadaptation, which they and others viewed as expressing a teleological bias.

Still, exaptations provide satisfying explanations based solely on present function, with no dependence on the future. Like atavisms, exaptations provide glimpses of the past, revealing former states and evolutionary transitions. Like atavisms, exaptations describe formerly functional traits that are now no longer needed. However, exaptations describe a distinctly different current function in present terms, whereas atavisms refer to reappearance of former traits whose function is no longer required (and therefore atavisms involve no adaptive shift in function, just a loss). Nonetheless, exaptations show how developmental shifts link to structural and functional shifts, and how these may depend on simple genetic tweaks.

Apoptosis (programmed cell death) is another important developmental process that can, by minor genetic alteration, profoundly influence the course of evolution—for example, by explaining how paddle-like limb buds can become hands and feet bearing multiple digits or, alternatively, webbed structures with digits still connected by sheets of tissue, depending on whether the cells between digits die or live.

Induction is another essential developmental process whereby contact between clusters of embryonic cells or tissues substantially alters the growth and differentiation of adjacent cells by production and diffusion of morphogens, chemical agents (such as retinoic acid) that prompt developmental changes. Induction plays crucial roles in the formation of the chordate neural tube (induced by the notochord) and the optic cup and lens (induced by the optic vesicle). Like homeosis, induction via precisely timed and located homeotic gene control cascades has been shown to play a major role in setting up basic body axes in fruit fly larvae. Like rigged coins, these larvae can be induced to grow with two heads or two tails depending on which specific chemicals accumulate at specific times and places during embryonic development.

Of course, it is not merely genetic tweaks that produce major differences in organismal form. Epigenetic factors, including the environment as well as interactions between different genes, also play major roles in determining traits. Emerald moths of the species Nemoria arizonaria have two generations per year. Larvae (caterpillars) that hatch in the spring feed on tiny flowers in oak catkins, and they grow to resemble those lumpy, golden-brown florescences (Greene, 1989). Caterpillars of the second generation feed instead on less nutritious oak leaves, after the flowers have disappeared and leaves emerged later in the growing season. These second-generation larvae resemble smooth, grayish oak twigs; they live on the same trees (later in the year) but look nothing like earlier caterpillars. It is thought that a chemical in oak leaves induces summer caterpillars to develop their twig-like form, although differences in ambient temperature during development may also play a role, just as offspring of turtles and other reptiles develop as males or females based on temperature differential.

In another striking example, Osterauer et al. (2010) documented that exposure to platinum inhibits prevents shell growth in young snails, causing snails to grow into shell-less gastropod molluscs nearly identical to slugs. This surprising finding naturally suggests that an equally minor single-gene modification, or epigenetic interaction, could have led shell-less slugs to develop, and evolve, into shelled snails. The ramifications of such easily tweaked events in roughly or finely tuning organismal phenotype, and therefore in changing the course of evolution, must be highlighted (Werth, 2014; Werth and Shear, 2014).

It cannot be overemphasized how consequential single gene tweaks can be in determining phenotype, even in complex organisms. Just as mighty oaks grow from tiny acorns, evolution's entire path can turn on tiny changes. Freitas et al. (2012) showed how overexpression of the hox13a gene in zebrafish, *Danio rerio*, causes fin reduction and proliferation of distal cartilage similar to that seen in the digital arch of tetrapod limbs. Freitas et al. (2012) also showed that same gene promoter, a 5' Hoxd enhancer, CsC, is involved in turning embryonic limb buds into fish fins or tetrapod hands. Might this, or a similar mechanism, have been the starting point for the first amphibious vertebrates that crawled ashore? Martin and Courtier-Orgogozo (2017) summarized a list of major phenotypic changes, behavioral as well as morphological, caused by mutations in regulatory signaling genes, including tooth number, armor plating, and schooling behavior in fish; muscle and fat growth and deposition in various mammals; wing size in insects; and pigmentation in numerous invertebrate and vertebrate species.

Such developmental constraints mean that evolutionary outcomes are limited, which likely explains why convergence is so common (Losos, 2018).

Case study: Humans as tail-less, upright talking apes

Major evolutionary modifications occurred not only in oaks, snails, and fish, but in our own species as well. Further, empirical evidence (Werth, 2009, 2013) confirms that a concerted emphasis on human-based case studies lead to greater student understanding of evolutionary mechanisms. Data from student outcomes illustrate the success of this teaching methodology. When asked how humans differ from other species, student response invariably involve two major changes: erect bipedalism and complex, vocalized language. This provides an unparalleled opportunity to show how minor genotypic changes can create major phenotypic shifts.

A post-anal tail at some stage of the life cycle is one of the six diagnostic characteristics of all chordates. Only two groups of vertebrates, anuran amphibians (frogs and toads) and apes, lack a tail as adults (Glick, 2020). Recent findings confirm that tail loss in apes involves a single mutation in the TBXT gene (Melchor, 2021; Xia et al., 2021; Vogel, 2021; Zimmer, 2021) which rendered new modes of locomotion, upright and knuckle-walking and brachiation, more efficient. Thus, the human family, Hominidae, began its course with a single mutation promoting our upright, bipedal stance. Zimmer (2021) reports that Russian geneticist Nadezhda Dobrovolskaya-Zavadskaya implicated this gene in tail loss in mice a century ago, in 1923.

Further, there is much evidence that *FOXP2* mutations fostered vocal changes in many animal lineages, including avian mimicry and birdsong, bat echolocation, and vocalization in mice, humans, and other mammals (Enard et al., 2002; Enard, 2011; Held, 2017). Additional studies have linked *FOXP2* mutations to cranial and brain expansion (Cofran and DeSilva, 2015; Boughner and Rolian, 2016; Fisher, 2019). Together, these robust findings suggest that speech, the other hallmark of humanity, likely traces its origins (like bipedalism) to a few key mutations.

Finally, there is considerable evidence that neoteny—retention of juvenile features in adults—has led to striking morphological and behavioral changes in humans and hominin ancestors (Bufill et al., 2011; Somel et al., 2012; Benitez-Burraco et al, 2020) and in other social species, notably in the evolution of dogs from wolves (Trut and Kharlamova, 2020; Zhang et al., 2020). Once again, we see remarkable phenotypic change arising not from slow accumulation of structural mutations, but instead from key regulatory mutations: the underlying basis of evo-devo. Mutation of a single gene, promoter, or transcription factor leads to potentially big changes in gene expression (Reno, 2015; Neubauer and Gunz, 2018; Diogo, 2018, 2020; Diaz, 2020).

Results of pedagogical investigation

When presented with these simple yet stirring stories, students are invariably struck by the unalterable truth of how single gene mutations have enormous impacts (Werth, 2014). Coupled with other recent findings showing that the total number of genes in the human genome is much lower than was once expected (Haussler, 2006; Schaefer et al., 2021), and that just 1.7-7% of the human genome is uniquely ours (Charles, 2021), these results demonstrate conclusively that our species is just a few steps away from other living things. This is a powerfully profound recognition that changes students' comprehension of evolutionary

pattern and process, and likewise changes their appreciation for what it means to be human. Analysis of this pedagogical approach, based on student surveys and learning outcomes (i.e., correct answers on objective and written exam questions; Werth, 2009, 2013) confirms that a concerted focus on evo-devo concepts, and particularly an explanation of how minor genotypic alteration often leads to major phenotypic shifts, pays big dividends (Reno, 2015; Diogo, 2018, 2020; Diaz, 2020).

Conclusions

In the famous words of Leigh Van Valen (1973), "Evolution is the control of development by ecology." Which individuals and species best survive and reproduce depends greatly on their phenotype, which in turn shapes, and is shaped by, interactive evo-devo connections. Although the phenotypic effects can be both complex and far-reaching, the underlying genetic causes can be stunningly simple and minor.

This discovery carries profound implications for educators. The key, as is often the case, lies in how instructors present nuanced material. Students and laypersons alike readily accept the "gene for X" concept, which is both harmful, in that the concept bears little relevance to most complex traits of interest, yet at the same time potentially helpful, in that one simple mutation in a regulatory gene can truly lead to big shifts in phenotype. *This does not mean the traits themselves are encoded by a lone gene*. Rather, one must appreciate the role of gene regulators in triggering, or suppressing, the expression of a symphony of genes. To offer a corresponding analogy, one can, with the flick of a single switch (or swipe of a smartphone screen) activate many different lights within one's home. Each light is a distinct and complexly built structure; many display variable activation, via dimmer switches. Nonetheless, the basic control of individual lights—*or even of all of them together*—can occur via one tiny mechanism.

As another analogy, consider that a single swing of a hammer cannot instantaneously construct all the multitude of elements within a house. However, the single swing of a hammer-like gavel at a foreclosure auction or zoning meeting can readily determine whether that house is built. Construction of the final structure seems, rightly, to be inordinately complex, but the ultimate determination of whether that structure will ever exist could turn on an instantaneous and even random event. Major outcomes hinge on simple, unexpected, and often contingent causes, not only in real estate but also in the world of nature. Put another way, evolution is not always a steady slog. It can be a sprint as much as a marathon. It pivots on tiny changes.

As Kampourakis and Minelli (2014) assert, evo-devo teaches that evolution depends not so much on the evolution of adult phenotypes as of their developmental mechanisms. Therefore, we should worry less about how adult form A might have evolved into adult form B, and instead focus on how their shared, underlying molecular and embryonic processes produce startlingly different outcomes with the barest molecular nudges (Hiatt et al., 2013). This fundamental developmental plasticity produces equally broad and central evolutionary plasticity, and with it, corresponding phenotypic disparity and organismal diversity. Just as the philosophers, and your grandparents, might have told you: it's often the simple things that make the biggest difference.

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