

# The Evolutionary Geometry of Human Anatomy: Discovering Our Inner Fly

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The human body is one still frame in a very long evolutionary movie. Anthropologists focus on the last few scenes, whereas geneticists try to trace the screenplay back as far as possible. Despite their divergent time scales (millions versus billions of years), both disciplines share a reliance on a third field of study whose scope spans only a matter of days to months, depending on the organism. Embryology is crucial for understanding both the pliability of anatomy and the modularity of gene circuitry. The relevance of human embryology to anthropology is obvious. What is not so obvious is the notion that equally useful clues about human anatomy can be gleaned by studying the development of the fruit fly, an animal as different from us structurally as it is distant from us evolutionarily. The underlying kinship between ourselves and flies has only become apparent recently, thanks to revelations from the nascent field of evolutionary developmental biology, or evo-devo. All bilaterally symmetric animals, it turns out, share a common matrix of body axes, a common lexicon of intercellular signals, and a common arsenal of genetic gadgetry that evolution has tweaked in different ways in different lineages to produce a dazzling spectrum of shapes and patterns. Anthropologists can exploit this deep commonality to search our genome more profitably for the mutations that steered us so far astray from our fellow apes.

Some of the greatest revelations in the history of science have involved uncovering linkages between superficially dissimilar entities.<sup>1</sup> For instance, Newton showed that the moon is just an oversized apple

ejected so forcefully that its parabolic trajectory became an ellipse, though the unity of parabolas and ellipses (as conical sections) had been noted long before by Euclid. Faraday proved that electricity and magnetism are not so different after all, and Maxwell added light to this spectrum.<sup>2</sup> Einstein wedded energy to mass on the one hand and space to time on the other, and the counterintuitive marriages in quantum mechanics go on and on.

For more than a century, the pithiest insight in biology was Darwin's heretical assertion that Man is an ape,<sup>3</sup> but in the last few decades evidence has been mounting for what may be the strangest linkage of them all. Our genome encodes our anatomy in much the same way as do the genomes of all other bilaterally symmetric animals, even those that are seemingly as different from us

as two-winged, six-legged, bug-eyed fruit flies.<sup>4</sup> The practical implication of this abstract realization is that we can apply the trove of insights that we've gleaned from 100 years of fly genetics to better understand human genetics.<sup>5</sup>

The discoveries that unveiled this unity of body plans are briefly recounted here under the rubric of "epiphanies," a term that is apt only insofar as it denotes a qualitative change in our thinking akin to Thomas Kuhn's "paradigm shift." No religious connotations are intended, nor should the term be construed to imply a "punctuated" view of history in which undue credit is given to scientists who happened to fit the last piece of a particular puzzle into place. Yes, there are heroes but, as Newton himself so humbly observed, they always stand on the shoulders of giants. To retrace the entire totem pole of those giants would require more space than is available here, so readers are referred to excellent reviews elsewhere.<sup>6–9</sup>

## THE MORPHOGEN EPIPHANY

In 1969, Lewis Wolpert<sup>10</sup> theorized that embryos assign particular structures, such as eyes versus ribs, to definite places in the body, such as the head as opposed to the thorax via gradients of diffusible chemicals. He called those chemicals morphogens to signify their role in generating morphology (anatomy). Just as you can tell how far you are away from an oncoming train by the perceived loudness of its horn, Wolpert argued that embryonic cells can tell how far they are away from a refer-

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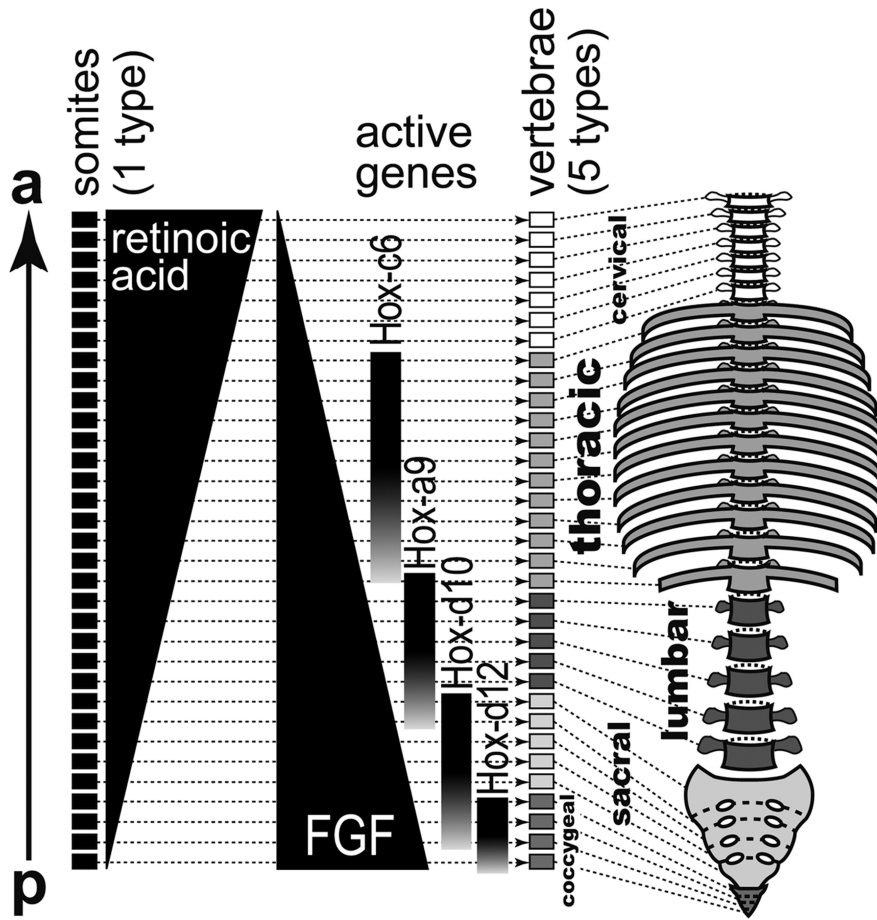


Figure 1. How morphogens specify vertebrae along the anterior-posterior (a-p) axis of the human body. (Figures 3 and 4 show how the other two axes develop.) Vertebrae develop from precursors called somites (black rectangles at left), which all look alike. Eventually the somites make the five types of vertebrae. The process that makes them different is shown from left to right. Retinoic acid, a derivative of vitamin A, is emitted from the anterior pole and the protein fibroblast growth factor (FGF) diffuses from the posterior pole. As they diffuse, their intensity declines so that their concentration at equilibrium describes a triangle. Somites can assess their location by sensing the amount, absolute or relative, of the morphogens. Why are two (reciprocal) gradients used when one should suffice? Gradients tend to be exponential rather than linear, as depicted here, so the high end of each gradient may compensate for the low signal-to-noise ratio at the tail end of the other gradient.<sup>11</sup> Alternatively, the cells may actually compute a ratio. These morphogens trigger the activation of specific *Hox* genes at different concentration thresholds. Finally, the products of these *Hox* genes or their combinations encode different vertebral types. Dramatic confirmation of this model comes from inducing *Hox-c6* expression along the entire spine in mice, which converts them into an eerie imitation of snakes, with ribs sprouting from cervical and lumbar vertebrae as well as thoracic ones.<sup>81</sup> Another recent insight concerns the excess cervical vertebrae in sloths.<sup>82</sup> Other bilaterally symmetric phyla also use *Hox* genes to establish "area codes" along their a-p axis,<sup>24</sup> so the genetic circuitry must predate the divergence of those phyla ~500 million years ago (the Homeobox Epiphany). Flies use a different morphogen (bicoid) to activate *Hox* genes along their a-p axis (not shown).<sup>44</sup> There are fewer than 10 universal morphogen families, suggesting not only great antiquity, but also tremendous versatility.<sup>4</sup> Redrawn from Held.<sup>28</sup>

ence point or line by the concentration of the morphogen that emanates from that point or line. The closer the cell is to the source, the stronger the signal should be, and the intensity should wane with distance as ei-

ther a linear or exponential gradient. If each axis of an embryo were to be spanned by a different gradient, then the three gradients would constitute a Cartesian coordinate system, and each cell would acquire a unique (x,

y, z) address or "positional information."

As farfetched as Wolpert's idea of chemical coordinates seemed at the time, he turned out to be basically right.<sup>11</sup> We humans are built via three orthogonal axes that are calibrated by scalar dosages of diffusible chemicals (Fig. 1). The nature of those chemicals has since been ascertained, though their modes of action are still being investigated. Other bilaterally symmetric organisms use grossly similar mechanisms.<sup>12</sup>

The first proof of a morphogen came in 1988 along the head-tail axis of the fruit fly.<sup>13</sup> Over the next decade, it began to dawn on researchers that all animal phyla employ a common set of five or so morphogens in a hierarchical way. Initially those chemicals are deployed along body axes,<sup>12</sup> but later they are reexpressed within particular organs to establish the fates of individual structures on a much smaller scale.<sup>14</sup>

For example, one of the cardinal morphogens is sonic hedgehog (Shh). In humans it diffuses from our nasal region toward our ears along the midline-to-lateral (ventral-dorsal) body axis, and assigns identities to intervening tissues.<sup>15</sup> Later, this same Shh molecule is secreted along the outer edge of each of our hands.<sup>16</sup> As it diffuses toward the inner edge, the ensuing gradient gives each finger a unique identity (pinkie, ring, middle, pointer, thumb).<sup>17</sup> If Shh malfunctions, then babies are born with a cyclops deformity, in which the two eyes merge at the midline,<sup>18</sup> and an "all thumbs" anomaly, in which all the fingers look like thumbs.<sup>19</sup> Both of these phenotypes are relevant to anthropology because interocular distances<sup>20</sup> and thumb lengths<sup>21</sup> figured prominently in primate evolution as adaptations, respectively, for depth perception and object manipulation. Incremental mutations in Shh pathways may have helped steer these organs in those directions.<sup>22,23</sup>

### THE HOMEBOX EPIPHANY

The nearly universal use of Shh and other morphogens among ani-

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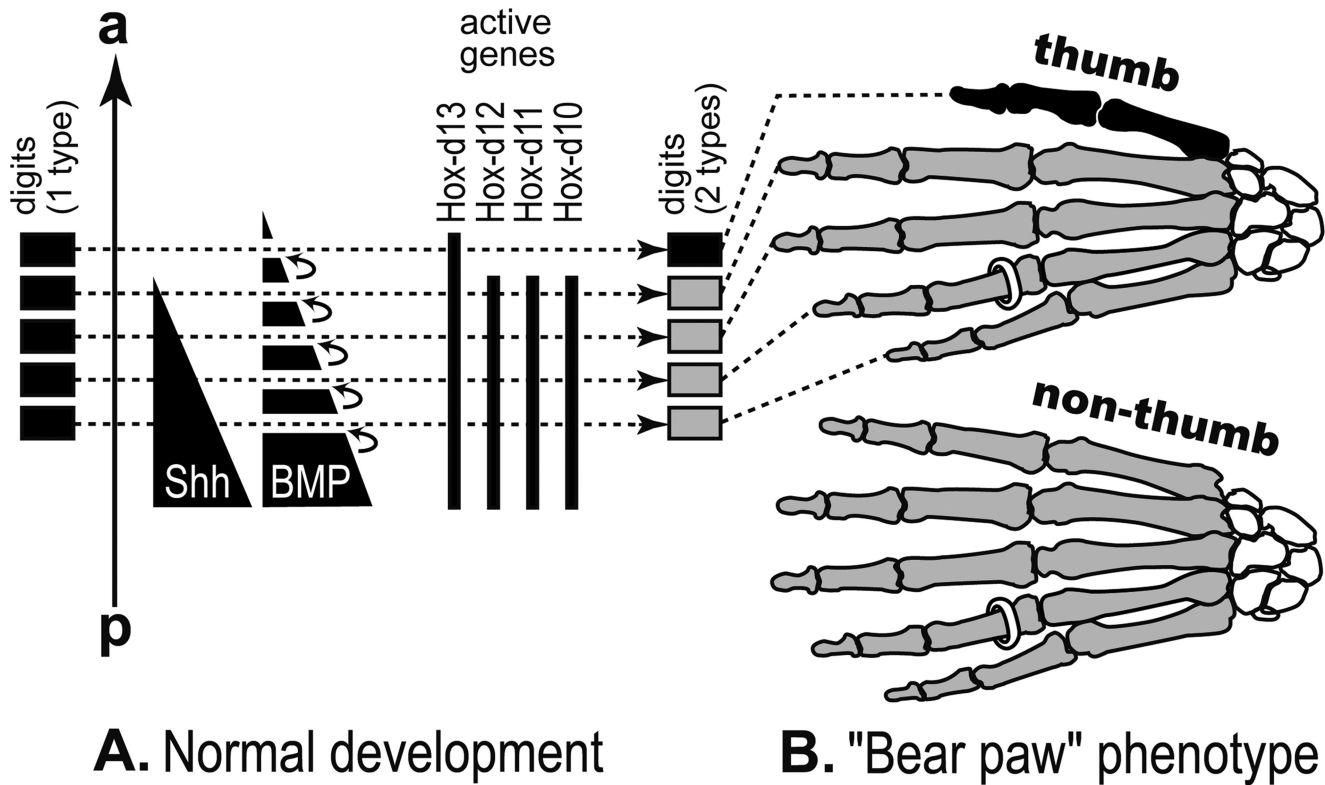


Figure 2. How morphogens specify digit identities across our palm (A) and an example of how mutations can transform our thumb (B). Modified from Held.<sup>28</sup> **A.** Differentiation of digits along the axis of a left hand during normal development. Digits develop from condensations (black rectangles) of cartilage-producing cells that all look alike.<sup>83</sup> The thumb becomes unique by the stages along the dashed arrows. First, the morphogen Shh is emitted by cells near the future pinkie.<sup>84</sup> Shh diffuses as far as the forefinger to form a gradient (black triangle).<sup>85</sup> Then the cells between the future digits measure the duration of their exposure to Shh<sup>86</sup> and secrete a proportional amount of the secondary morphogen, bone morphogenetic protein (BMP), which comprises types 2, 4, and 7 (not numbered here).<sup>87</sup> BMP is thought to diffuse a short distance anteriorly to activate *Hox* genes in the adjacent digit.<sup>88</sup> If *Hox-d13* is expressed above a low BMP threshold, whereas *Hox-d10*, *-d11*, and *-d12* require a higher threshold, then the most anterior digit acquires the code "0001" ("1" denotes activity and "0" inactivity for *Hox-d10*, *-d11*, *-d12*, *-d13*) and goes on to become a thumb. The other digits are assigned "1111" and become ordinary fingers. We do not yet know how the thumb's 0001 *Hox* code dictates its anatomy (two phalanges, opposability).<sup>17</sup> We also do not know how the effector genes were tweaked during hominin evolution to make our thumb the longest of any primate relative to the index finger.<sup>89</sup> **B.** Tracing of a radiograph of the left hand of a woman seen at an obstetric clinic in Austria in 1957.<sup>33</sup> On both hands, thumb was transformed into a forefinger.<sup>34</sup> According to the clinical report, all thumb-specific muscles and tendons were missing and the digit was not opposable. This "bear paw" phenotype is reminiscent of a preprimate mammal, but we do not know whether the abnormality is a true atavism. Her baby, born at the clinic, also had the thumbless, five-finger phenotype, so the condition is probably genetic, though the mutation was never mapped. In mice a similar phenotype can be induced by forcing expression of *Hox-d12* in the thumb region.<sup>90</sup>

mal phyla implies that these phyla inherited a "tool kit" of signaling pathways from a common ancestor who lived more than 500 million years ago.<sup>24</sup> Another part of that tool kit soon became apparent.

Beginning in 1984, a family of related genes began to be documented in phyla whose members manifest bilateral symmetry in their anatomy. Each such gene contains a 180 base-pair sequence called the homeobox.<sup>25</sup> Clusters of *Hox* (Homeobox) genes were found to record positional information in a way that resembles the way that com-

puters store data. As the concentration of a morphogen rises within a gradient, the *Hox* genes within a cluster are turned on sequentially at different thresholds. The combination of their binary on/off states encodes the (analog) morphogen signal as a digital memory that endures long after the morphogen vanishes. Like the limited menu of metazoan morphogens, the *Hox* complexes can also be traced back to a precambrian ancestor.<sup>24</sup>

The original role of the primordial *Hox* gene cluster appears to have been to provide "area codes" for the

head-tail axis of the body.<sup>26</sup> In fruit flies, these codes distinguish different body segments and their appendages, including legs, wings, and antennae. In humans, the codes denote different classes of vertebrae: cervical, thoracic, lumbar, sacral, and coccygeal (Fig. 1).

*Hox* codes may ultimately provide answers to some nagging questions about primate evolution. For instance, tail loss in the transition from monkeys to apes may have been due to posterior *Hox* genes having accidentally snagged target genes that stymie growth,<sup>27,28</sup> as in tailless

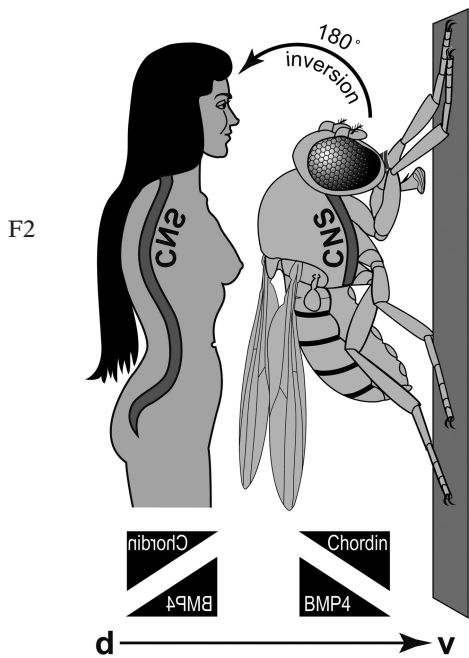


Figure 3. How morphogens demarcate territories along the dorsal-ventral (d-v) body axis. The morphogen bone morphogenetic protein (BMP4) is emitted from our ventral midline when we are embryos; its inhibitor, chordin, diffuses from our dorsal midline.<sup>12</sup> (An adult is shown here for orientation.) All other bilaterally symmetric phyla studied thus far use these same signals but with an opposite polarity.<sup>91</sup> For example, flies emit a BMP4 homolog (Dpp) from their dorsal midline and a chordin homolog (Sog) from their ventral midline.<sup>12</sup> Evidently, the founder of our phylum flipped over like a swimmer switching from breaststroke to backstroke, and we have been upside-down relative to all of the other phyla ever since (the Inversion Epiphany).<sup>92</sup> (A fly is used here as a proxy for that preinversion protochordate because we don't yet know what it looked like.) An inversion of this kind was actually proposed in 1822 by Geoffroy St. Hilaire, based in part on the fact that our central nervous system (CNS) is on the opposite side from that of an arthropod (for example, a fly).<sup>38,93</sup> Apparently, the CNS arises at a low BMP4 dose regardless of the phylum, a legacy of our common ancestor.<sup>94</sup> The genes activated by BMP4 (not shown) are also conserved<sup>12</sup> but are not *Hox* family members.

breeds of dogs<sup>29</sup> and cats.<sup>30</sup> Likewise, the reshaping of our spine during the transition to bipedalism may have been due to various *Hox* genes having captured target genes that bias growth to one side of the vertebral column or the other (dorsal versus ventral), thus evoking curves where none had existed before.<sup>28,31</sup>

Over the eons, our axial *Hox* “memory boards” have also been recruited to function within various individual organs at later times in development. For example, one subset of *Hox* genes governs the identities of our fingers within the *Shh* gradient (Fig. 2A). The code for our thumb is “*Hox-d12* off; *Hox-d13* on,” whereas all our other fingers use “*Hox-d12* on; *Hox-d13* on.” Somehow this code allows our thumb to make two instead of three phalanges.<sup>32</sup> Studies of how these *Hox* master genes control growth-affecting target genes may eventually reveal how anthropoids sculpted an opposable thumb from an ordinary digit.<sup>21</sup>

Mutations that alter the *Hox* code can apparently reverse that sculpting, that is, they can convert a thumb back into an ordinary finger. Triphalangeal thumbs occur occasionally, but do not typically entail any loss of the muscles for opposability.<sup>22</sup> The only total transformation of both thumb bones and muscles ever described was recorded at a clinic in Austria in 1957.<sup>33</sup> A mother and her newborn had the same thumbless, five-finger (“bear paw”) phenotype (Fig. 2B).<sup>34</sup> She told her obstetrician that she never thought of her oddity as a disability since it proved helpful in playing the piano. Its genetic basis was never analyzed, but may have involved a mutant *Hox* gene.<sup>21</sup> A related problem for anthropologists is how our great toe lost its opposability (to enhance its leverage) as hominins became bipedal? Work now under way may soon pinpoint the mutations responsible for this reconfiguration as well.<sup>35</sup>

### THE INVERSION EPIPHANY

In the 1990s, another concordance among bilaterally symmetric animals was genetically documented.<sup>36</sup> The chemical signals that establish the dorsal (back) side of a fly were found to specify the ventral (belly) side of chordates such as humans, and vice versa.<sup>37</sup> This correlation confirmed a seemingly discredited and much maligned hypothesis that had been proposed in 1822 by Geoffroy St. Hilaire.<sup>38</sup> He had conjectured, based on anatomical evidence, that chordates are upside-down versions of

arthropods.<sup>39</sup> Recent data confirm that, indeed, a basal chordate must have inverted its dorsal-ventral axis (Fig. 3),<sup>40</sup> like a swimmer flipping from breaststroke to backstroke, and our phylum has retained this exceptional orientation ever since.

Added to the previous insight about *Hox* codes along the head-tail axis, this new realization about the dorsal-ventral axis meant that flies and humans share at least two coordinates in common. Even our third axis, the left-right dimension, may turn out to rely on a shared genetic mechanism involving the gene *nodal* (Fig. 4).<sup>41</sup> This Cartesian congruence implies that the overt anatomical differences between our species (exoskeleton versus endoskeleton, 6 versus 2 legs, compound versus simple eyes) are only skin deep. Our covert molecular scaffolding is remarkably the same.

This underlying unity suggests that the “operating systems” of our two genomes may be more alike than anyone had ever guessed.<sup>42</sup> Hence, anthropologists might actually be able to glean some useful clues about the logic and evolution of the human genome by studying the inner workings of the fly's genome.<sup>5</sup> It is ironic that the first animal genomes ever sequenced were those of flies and humans, both of which were announced in 2000.<sup>43</sup> On this 10th anniversary of those achievements, it is fitting that we should look afresh at the potential benefits of exploiting this equivalence.<sup>44</sup>

### HUMAN HAIR VERSUS FLY BRISTLES

To appreciate the heuristic utility of the fly-human analogy, consider a familiar mystery. Why did our hominin ancestors become naked compared to our fellow apes?<sup>45</sup> The most likely explanation is that hair loss prevented overheating during running.<sup>46</sup> But there is a neglected aspect to this story: How did our hair loss happen *genetically*? No one knows which genes were mutated.

This riddle is complicated by the fact that we did not lose our hair randomly. We kept an abundance on

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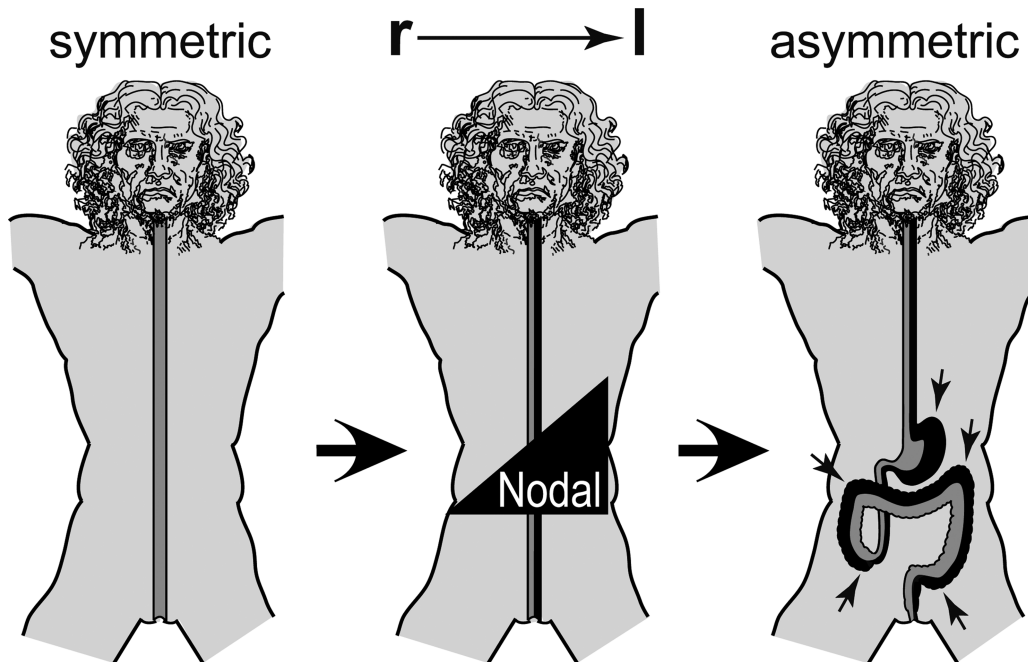


Figure 4. How a morphogen establishes asymmetry along the left-right (l-r) body axis. As embryos, we start out symmetric, as shown here for our gut. (An adult torso is shown for simplicity.) Later (second panel) the morphogen nodal intensifies on our left side due to a leftward flow of signals propelled by rotating cilia (not shown)<sup>95</sup> and activates certain genes (black half of the gut). Presumably, those left-right genes, in combination with genes expressed along the a-p axis (*Hox?*),<sup>96</sup> then cause excess growth at specific “area codes” (arrows) on the left side of the gut, culminating in the fundus bulge of the stomach and square corners between the ascending, transverse, and descending colon.<sup>28</sup> The 270-degree arc per se (the shape of a question mark) arises mainly from twisting of the midgut during its return to the abdomen from the umbilicus in the 10th week of gestation.<sup>57</sup> (The small intestine and accessory organs are omitted for clarity.) Why should our gut (~10 m) be so much longer than our torso (~1 m)? Nutrients are absorbed through the gut lining (2-d area) before being circulated to the body (3-d volume).<sup>97</sup> As body size increased during chordate evolution, the demand for nutrients (body volume) scaled up by the cube of our linear dimensions, while the rate of supply (intestinal area) rose by only the square. Hence, any mutations that lengthened the gut would have been favored since they alleviated this discrepancy. Note that nodal, in its role as a symmetry breaker, is acting like a switch rather than as a morphogen *sensu stricto*.<sup>98</sup> The morphogens nodal (l-r axis) and BMP4 (d-v axis) are both members of the TGF $\beta$  family of signaling molecules.<sup>99</sup> Adapted from Held.<sup>28</sup>

our scalp, armpits, and groin and we saved a dash here and there for our eyebrows, eyelashes, and nasal passages. Men still grow a fair amount on our chests and backs after puberty. So the challenge we face is to figure out not only how the overall amount of hair was reduced, but how it was retained in certain places.

If we focus on this underlying issue of spatial patterning, then the question becomes: How is our skin mapped within our genome? Here is where the fruit fly can be of some use. Flies are covered with bristles, and we know the genetics of bristle patterning in exquisite detail.<sup>44</sup> Even though fly bristles are not homologous to human hairs, we can still learn something about how the fly skin is mapped in its genome.<sup>47</sup>

Flies allocate bristles to certain skin areas via a command center that spans 100 kilobases of DNA. Within this bris-

tle headquarters (BHQ) there are two master genes, *achaete* and *scute*, and eight control elements, or *cis*-regulatory enhancers, that direct their expression to specific sites in the skin. So far, the BHQ sounds a lot like the *Hox* complex. However, unlike the *Hox* complex, where the order of genes matches the sequence of body regions along the a-p axis, the order of enhancers in the BHQ is scrambled with respect to the territories they designate. The same scrambling is seen in stripe-control genes that establish the pattern of segments in the fly embryo.<sup>48</sup> Indeed, the colinearity of *Hox* genes turns out to be the exception rather than the rule for patterning mechanisms. Hence, we shouldn't expect to find a hair “homunculus” in our genome.

Do humans have a Hair Headquarters (HHQ) like the fly's BHQ? If so, how can we find it? Based on what we

know about the BHQ, we should look for a signaling pathway that increases hair density when overstimulated and decreases hair density when incapacitated. Experiments of just this sort have been done in mice. Among the signaling pathways shared by all bilaterians, the Wnt pathway presents itself as the most likely candidate. Overexpression of the Wnt transducer  $\beta$ -catenin causes excess hairiness in both embryos<sup>49,50</sup> and adults,<sup>51</sup> whereas blocking  $\beta$ -catenin during development prevents hair formation.<sup>52</sup> No other pathway evokes such traits.<sup>53</sup> Hence, the most likely place for the HHQ is a Wnt site. There are 19 such loci in our genome.<sup>54</sup>

Figure 5 sketches what our HHQ might look like, given what we know about the fly's BHQ. Obviously, we are playing a guessing game here, but it is *educated* guesswork because we are using the fly genome as a

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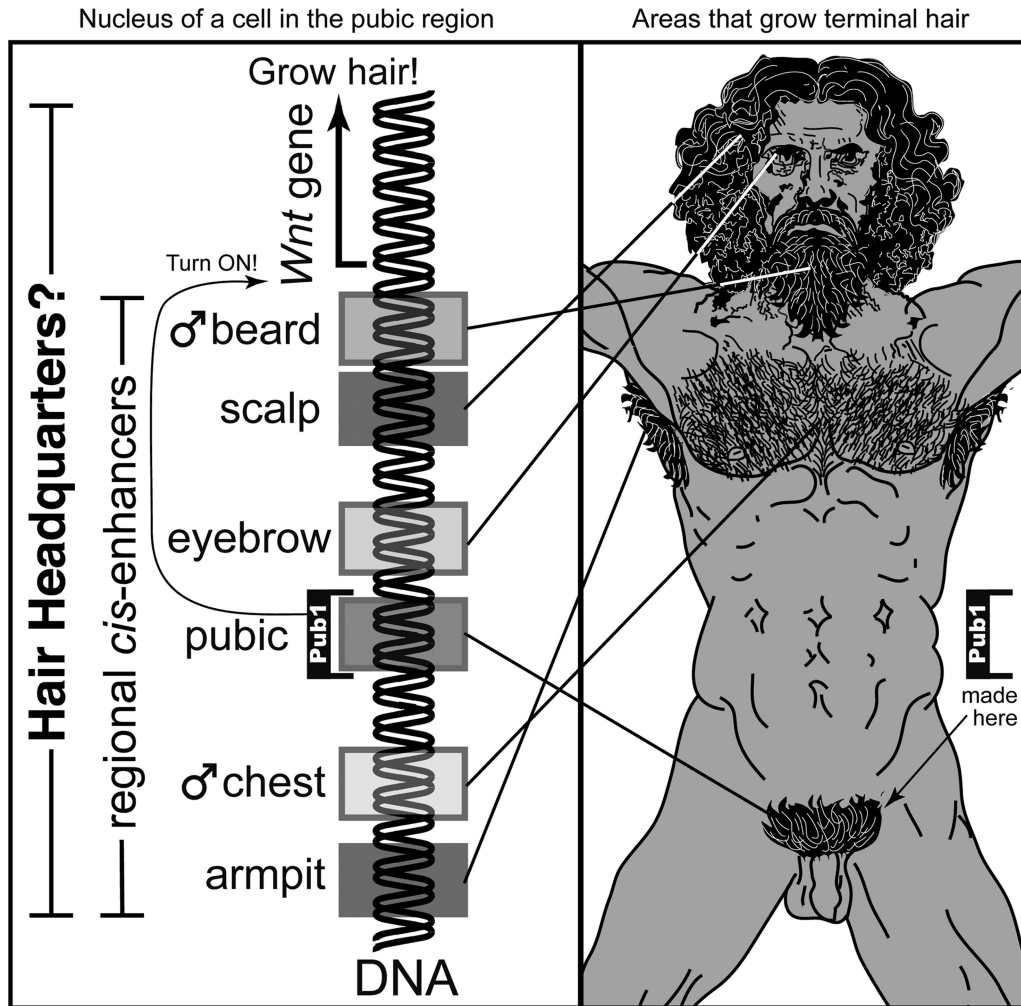


Figure 5. Imaginary rendering of what our Hair Headquarters (HHQ) might look like (if we have one), based on what we know about how flies use their Bristle Headquarters (achaete-scute complex).<sup>44</sup> Genetic experiments in mice indicate that the Wnt signaling pathway is chiefly responsible for promoting hair initiation.<sup>49–51</sup> There are 19 *Wnt* loci in humans (and mice), but we do not yet know which one, if any, serves as the master gene for hair formation. (Alternatively, the HHQ might be at a gene for a Wnt transducer, for example,  $\beta$ -catenin.) Six body areas (right) that make terminal hair (as opposed to peach fuzz “vellus”)<sup>100</sup> are mapped onto their DNA control elements (left), the order of which is scrambled. Any element (cis-enhancer) can cause transcription of the *Wnt* gene (bent arrow) if it is occupied by its matching protein. For example, suppose that a gene *Pub1* is transcribed in our pubic area and that its Pub1 protein binds the enhancer “pubic” in the HHQ. Such binding would turn on the *Wnt* gene and thus make hair. Proteins from other regions would activate *Wnt* via their own cognate enhancers. Because hominins evolved from a fur-covered ape, however, it is actually more likely that our HHQ involves negative (not positive) control. If so, then the actual enhancers (inserted one by one into the HHQ over millennia?) would correspond to *naked* parts of our body, such as the forehead and neck, and they would bind regional *inhibitors*. Adapted from Held,<sup>47</sup> where I delve into the puzzle of hominin hair evolution and the genetics of hair patterning in much more detail. (My apologies to Lenny for defacing his Vitruvian Man!)

roughly drawn “treasure map” to hunt for analogous circuitry in our genome. Only time will tell whether this approach will prove fruitful.

### ORGAN SHAPING VIA ORIGAMI FOLDING

One of the oldest insights to be learned from classical embryology was that gross anatomy arises via planar geometry.<sup>55</sup> Despite the fact that

animals are three-dimensional, we are actually built from two-dimensional sheets of cells that are folded in ritualized sequences. In humans, for example, our lens and inner ear both start as circular placodes that submerge to form hollow spheres.<sup>56</sup> Our spinal cord and digestive tract both begin as rectangular epithelia that roll up into hollow tubes during the fourth week of gestation.<sup>57</sup> Even our brain, which looks like a solid hunk of

marble, commences as a tube that inflates to become a hollow, crumpled balloon.<sup>58</sup> Nowhere is this origami analogy (that is, humans as folded sheets) more clear than in our abdominal cavity. Our large intestine bends itself at predictable right angles to form the ascending, transverse, and descending colon (Fig. 4), whereas our small intestine seems to meander randomly to fill the remaining space.<sup>57</sup>

Along our digestive tube, perpendicular hollow outgrowths occur at strategic points to form accessory organs, including our liver, pancreas, and gallbladder.<sup>59</sup> The smallest is our appendix. The largest are our lungs, which start as a tiny pouch that branches once to form the bronchi, then repeatedly to form a tree-like network that culminates in clusters of grape-like sacs, the alveoli, where gas exchange will eventually take place after birth.

Why should human embryos make a breathing tube off our digestive tube, considering that such a design puts us at risk of choking to death on food mistakenly swallowed down our windpipe? It would have been much safer to use a more direct route for importing air directly into our lungs. Until Darwin, no satisfactory explanation for such obvious flaws was available, since man was supposed to have been created in the image of a perfect deity.

Darwin's solution? We weren't created as land animals; rather, we evolved from aquatic ancestors. Lungs began as a pouch in fish, where it was employed to augment the intake of oxygen under hypoxic conditions, (such as in muddy waters). Obstruction of the pouch by food must have happened occasionally, but occlusions were not lethal because the fish still had gills with which to breathe. Only when one group of fish came onto land and evolved to become amphibians did choking become deadly because by then the gills had been discarded in the adult stage.

Thus, humans are essentially bipedal fish whose lung-gut linkage once worked well as a backup device but now has become a risky liability due to our reliance on that airway alone.<sup>60</sup> Many other examples of sub-optimal anachronistic features can be found throughout the human body.<sup>28</sup> They include the appendix, useless but dangerous, from our primate ancestors, as well as the birth canal, which worked splendidly until hominin brains expanded so greatly that the neonate head barely fit through the pelvic opening, risking obstetric crises for both mothers and infants.

If having lungs connected to our digestive tube is so clearly maladaptive, why didn't evolution ever remedy the problem? After all, how difficult could it be for mutations to simply move the "area code" for lung invagination from a spot on the digestive tube to a different spot on the external skin surface—say, somewhere on our neck?

Well, it might be difficult indeed. Here we have stumbled on the kind of knotty enigma that will tempt and torment human geneticists for decades to come. The question is one of evolvability: Why are certain changes genetically easy, while others are hard and still others are virtually impossible, given the limited time available for adaptation to occur?<sup>61</sup>

To answer such questions we will need to learn a lot more about the preferred modes of mutational change during evolution (cf. review of transposition in this issue of *Evolutionary Anthropology*),<sup>62</sup> the grammar of gene regulation,<sup>63</sup> and the logic of developmental pathways.<sup>64</sup> How was the original circuitry tweaked genetically over evolutionary time to reconfigure developmental processes so that an old structure could serve a new function?

Here again, flies help us in our quest. Fruit flies also do stupid things during their development, things that are worth studying genetically to see why they have never been repaired evolutionarily. The craziest of their stunts is a 360-degree rotation of the male genitalia, which has no net effect on the angle of the penis. In a recent study<sup>65</sup> the authors explain the situation as follows. A distant ancestor held the penis in a 12 o'clock orientation. Then an intermediate ancestor adopted a mating posture better suited to a 6 o'clock angle, whereupon the genital plate evolved a muscular ring that turned the prospective penis through 180 degrees. Finally, modern fruit flies reverted to the original posture and so had two options to return to a 12 o'clock angle; disable the rotation or continue it for another half turn. The latter route was taken, despite wasting energy, because the mutations that happened to occur and spread

were those that made a second muscular ring. Evidently, duplicating the ring module was easy. More such studies may help us figure out how our own genome took some equally silly turns in the past.

Lest anyone doubt the relevance (or elegance) of the work being done along these lines in fruit flies, readers should consult the research of Sean Carroll's team in Wisconsin.<sup>66</sup> They are systematically dissecting the spatial control of body pigmentation. Any of their recent papers would make a useful primer for ambitious geneticists who dream of someday reconstructing the history of hominin anatomical evolution one mutation at a time.

## IS EVOLUTION REVERSIBLE IN GENERAL?

The broader question raised by the preceding discussion is whether evolution is reversible in situations other than just origami sequences.<sup>67</sup> Atavisms are common in insects, but have been reported only rarely in humans.<sup>68</sup> The case of the thumbless, five-fingered hand (Fig. 2) is one putative example. Another is the rare appearance of stunted (monkey-like?) tails in human babies,<sup>69</sup> but these protrusions lack vertebrae, so they are probably not true reversals.<sup>70</sup> Of course, such cases are merely sports. The reversal of evolution *sensu stricto* in whole species is a much rarer occurrence.<sup>68,71</sup>

Another possible instance of an atavism in humans is excessive hairiness, the returning of our skin to a prehominin fur coat.<sup>69</sup> Various syndromes convert the invisible vellus ("peach fuzz") on various parts of our body into long terminal hair.<sup>72</sup> Many such traits have been traced to single mutations. The hairiest person ever described is a Chinese man with  $\geq 5$  cm hair covering 96% of his body.<sup>73</sup> His syndrome was mapped to a tiny DNA duplication on chromosome 17, but we do not yet know which gene or genes are responsible. That locus does not harbor a Wnt gene, so it is unlikely to be the master control center for hair patterning discussed earlier.<sup>47</sup>

One intriguing idea about human evolution was Louis Bolk's fetalization theory,<sup>74</sup> which was popularized by Stephen Gould in his *Ontogeny and Phylogeny*.<sup>75</sup> Bolk noticed that adult humans resemble baby chimps in the sparseness of our hair, the flatness of our face, and in other respects. Might evolution, he wondered, have retarded our rate of development so that we progress through the stages of ape maturation in slow motion? His theory fails to explain many trends in hominin evolution,<sup>76</sup> but it might help to account for why men grow chest and back hair later than pubic hair, and nose hair and bushy eyebrows later still.

The slowing down or speeding up of development, termed heterochrony,<sup>77</sup> can be achieved relatively easily by single mutations,<sup>78</sup> so Bolk's basic premise is at least plausible and potentially applicable elsewhere.<sup>79</sup> However, if retardation is so easy to do genetically, why hasn't it been equally easy to undo? That is, why has no human mother ever had a baby who matured quickly to atavistically resemble an adult ape in its fur covering, physiognomy, and so forth?<sup>78</sup> Regrettably, we understand even less about how our genome measures time than we do about how it charts space,<sup>77</sup> so it may be some time before we can answer this question in any meaningful way.<sup>80</sup>

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